Exhibit 120

22

Epidemiology of Commonly Used Statistical Terms and Analysis of Clinical Studies

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OUTLINE

KEY POINTS

1. Epidemiology is the study of distribution of disease and factors the determine disease occurrence in populations.
2. As much as possible, medical decisions should be based on quality evidence. The best evidence is a properly designed randomized controlled trial. Evidence from nonrandomized but well-designed control trials is of lesser quality. Next in reliability is well-designed cohort or case-control studies, which have been repeated by several investigators. Opinions of respected authorities and extensive clinical experience are least reliable.

EPIDEMIOLOGY

Epidemiology is the study of distribution of disease and the factors that determine disease occurrence in populations. The focus is on groups rather than the individual. Persons within a population do not have equal risk for disease occurrence, and the risk of a disease is a function of personal characteristics and environmental exposures. Patterns of disease occurrence within specific populations can be evaluated to determine why certain groups develop illness when others do not. The impact of epidemiology on gynecologic oncology is evidenced by the significance of studies such as the association with infection of oncogenic human papillomavirus and cervical cancer, obesity and the risk of endometrial cancer, and the risk factors for gestational trophoblastic neoplasia. Epidemiologic studies are unique in their focus on human populations and their reliance on nonexperimental observations. Epidemiologic methods are used in searching for causes of disease, disease surveillance, determining the cause of disease, diagnostic testing, searching for prognostic factors, and testing new treatments.

Because the quality of epidemiologic evidence varies greatly among studies, the scientific community endorses the principles of Sir Austin Bradford Hill, an eminent British statistician, when attempting to identify causal associations. A cause of a specific disease is an antecedent event or characteristic that is necessary for the occurrence of the disease (Box 22.1).

EVIDENCE-BASED MEDICINE

As much as possible, medical decisions should be based on quality evidence. The best evidence is a properly designed randomized controlled trial. Evidence from nonrandomized but well-designed control trials is of lesser quality. Next in reliability is a well-designed cohort or case-control studies, which have been repeated by several investigators. Opinions of respected authorities and extensive clinical experience are least reliable.

Physicians are currently encouraged to practice evidence-based medicine. This means that clinical trial evidence must pass statistically valid tests for conclusions to have meaning. Good science depends on accurate (ie, statistically significant and meaningful) data from clinical trials. The best trials are usually experimental, powered, randomized, and blinded. Patients randomly assigned to a treatment group or a control group must have an equal probability of being assigned to either group. This prevents selection bias (eg, putting healthier or better prognosis patients in one group and those with a poor prognosis or high likelihood of disease risk in another group). Blinding prevents patients, investigators, or statisticians from knowing who is in the control group and experimental group; thus, biased actions are avoided.

Whereas retrospective and observational studies are descriptive and do not involve either an intervention or a manipulation, an experimental study does. A prospective trial poses the

BOX 22.1 Strength of Association

1. Temporality: Exposure must precede the onset of the disease.
2. Dose-response: Risk increases as exposure increases.
3. Replication: The association is observed repeatedly.
4. Coherence: The association is consistent with other scientific knowledge and does not require that established facts be ignored.
5. Exclusion of the role of chance: Appropriate statistical tests demonstrate that the observed association is extremely unlikely to have arisen by chance.

Modified from Hill AB. The environment and disease: association or causation? Proc R Soc Med 1965;58:295.

TABLE 22.1 Mathematical Definitions of Statistical Terms

Terminology	Mathematical Definition
Prevalence rate	Number of persons with disease/Total number in the group
Incidence rate	Number of new cases/Total number at risk per unit of time
Kappa	$(P_{obs} - P_{chance})/(1 - P_{chance})$
Sensitivity	True positive/(True positive + False negative)
Specificity	True negative/(True negative + False positive)
Predictive value positive	True positive/(True positive + False positive)
Predictive value negative	True negative/(True negative + False negative)

question before the data are collected, thus allowing better control of confounding variables, unlike a retrospective study, which poses the question after the data are collected.

MEASURES IN EPIDEMIOLOGY

To describe and compare groups in a meaningful manner, it is important to find and enumerate appropriate denominators and statistical terms (Table 22.1).

- **Incidence rate:** Measures the new cases of a specific disease that develop during a defined period of time and the approximation of the risk for developing the disease. The incidence rate focuses on events. Incidence measures the probability of developing a disease.
- **Kappa coefficient:** Kappa indicates how much observers agree beyond the level of agreement that could be expected by chance. Kappa is estimated as $(P_{obs} - P_{chance})/(1 - P_{chance})$. Thus, the kappa coefficient is the observed agreement, corrected for chance as a fraction of the maximum obtainable agreement, also corrected for chance. Landis and Koch have suggested useful categorizations. Kappa = 0.00 should be taken as representing "poor" agreement, 0.00 ± 0.20 as "slight" agreement, 0.21 ± 0.40 as "fair" agreement, 0.41 ± 0.60 as "moderate" agreement, 0.61 ± 0.80 as "substantial" agreement, and 0.81 ± 0.99 as "almost perfect" agreement. A kappa coefficient of 1 represents perfect agreement.
- **Mean:** The average of a sample of observations.
- **Median:** The middle value when the values are arranged in order from the smallest to the largest.
- **Meta-analysis:** The statistical process of pooling the results from separate studies concerned with the same treatment or issue is frequently used in the context of medical statistics and provides the quantitative backbone of the evidence-based medicine program. A large number of meta-analyses are undertaken with the broad aim of combining divergent outcomes into a single estimate of treatment effect. For example, the Cochrane Collaboration endeavors to collate and synthesize high-quality evidence on the effects of important health care interventions for a worldwide, multidisciplinary audience and publishes them in the *Cochrane Database of Systematic* Reviews. Meta-analyses increase the statistical power by increasing the sample size, resolve uncertainty when reports do not agree, and improve the estimates of effect size. The bias of publication only of positive results is a concern for those using results of meta-analyses because, if statistically significant or "positive" results are more likely to be published, a meta-analysis based on the resulting literature will be biased. The quality of the studies included is important to the quality of the final result.
- **Pearson's correlation *r*:** The degree to which two variables are related is called correlation. Pearson's correlation is represented by the value r and varies between −1 and +1. It is usually presented as a scatter point graph. A value of −1 suggests a perfect negative linear relationship, a value of 0 reflects no linear relationship, and a value of 1 reflects a perfect linear relationship. Values of −1, 0, and +1 are rare.
- **Person time:** The sum of the observation period of risk for the persons in a group being studied.
- **Predictive value positive:** The proportion of positive test results that is truly positive (ie, the probability that someone classified as exposed is truly exposed). This value only refers to positive tests.
- **Predictive value negative:** The proportion of negative test results that is truly negative. The predictive value of a negative test result refers to the proportion of patients with a negative test result who are free of disease.

These values, unlike sensitivity and specificity, indicate the reliability of the test in the determination of presence or absence of disease.

- **Prevalence rate:** The amount of disease in a population. Prevalence measures the proportion of diseased individuals at a particular time and represents a snapshot of the disease. Other commonly used terms are *prevalence proportion* and *point prevalence*. It is a measure of status and includes individuals with newly diagnosed disease and those surviving with disease. The numerator is the number of affected individuals in a specific time period. The denominator is the total number of persons in the group. Prevalence rates range between 0 and 1.
- **Quality-adjusted life year (QALY):** The QALY was developed as an attempt to combine the value length of life and quality of life into a single index number. One year of perfect health is given a value of 1. Death is given a value less than 0. A year of less than perfect health will have a value less than 1. States of health considered worse than death can be argued to have a negative value. The QALY value is

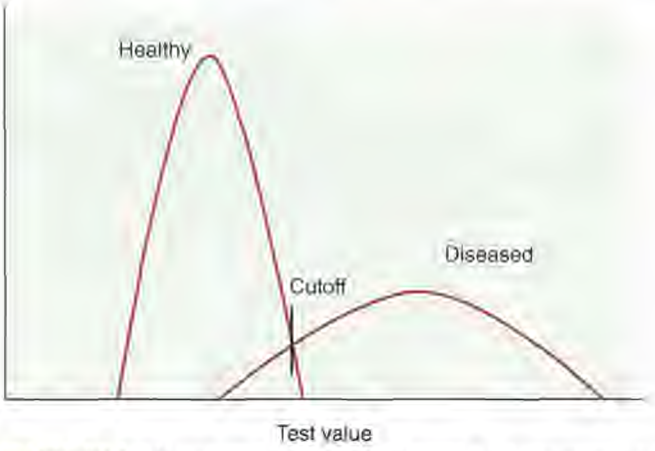

FIGURE 22.1 Effects of shifting cutoff point on sensitivity and specificity.

determined by multiplying the utility value associated with that state of health by the years lived in that state. QALY is a metric used to compare the benefit of health care interventions. Combination of QALYs with the cost of an intervention (Cost/QALY) can provided an economic framework for comparisons of therapies. QALYs have several limitations and should not be used alone in decision making.

- **Sensitivity:** The proportion of truly diseased persons who are classified as diseased by the test. The sensitivity of a test is therefore the probability of a test being positive when the disease is present. The sensitivity of test may also be called the true-positive rate. In Fig. 22.1, it is evident that the cutoff point of a test can affect the sensitivity. If the cutoff point is moved to the left, more diseased persons will be identified. At the same time, more healthy persons will be erroneously classified as sick. However, as the cutoff value for normal is moved to the right, the test will become less sensitive because fewer diseased persons will be classified as such.
- **Specificity:** The proportion of a population of disease-free individuals who are classified as undiseased by a test. In contrast to the sensitivity of a test, the specificity of a test is the probability that a test result will be negative when the disease is absent. The cutoff point of a test for normality influences the specificity. As the value of normality or cutoff moves to the left, the test becomes less specific because fewer health individuals are recognized as such. In contrast, moving the cutoff values to the right increases the specificity (see Fig. 22.1). In the best scenario, a test would be able to discriminate between diseased and healthy individuals without any overlap. **More often, the scenario is as presented in Fig. 22.1, in which there is significant overlap and whatever the cutoff value healthy persons may be classified as diseased and sick persons classified as healthy.** When we set the cutoff point for a test, we must be attentive to the purpose of the test. If the disease is treatable and missing the disease has serious ramifications, then we must favor sensitivity over specificity. Alternatively, if it is more important to correctly identify healthy individuals, then specificity is prioritized. Published reports of the performance of tests usually just provide sensitivity and specificity results. Variations of these measures occur under many conditions and will also produce variations in predictive values.
- **Standard deviation (SD):** A measure of the variability within each group. If there is a normal (bell-shaped curve) distribution, approximately 95% of the values are within 2 SDs on both sides of the average.
- **Tests of heterogeneity:** Before performing a meta-analysis, it is customary to assess evidence of variation in the underlying effects. This variation, termed "heterogeneity," arises because of differences across studies in populations, exposures *or* interventions, outcomes, design, or conduct. A forest plot is useful for visual assessment of consistency of results across studies. A statistic that measures the consistency of findings as the proportion of total variation in point estimates attributable to heterogeneity is now widely used.

ANALYSIS OF CLINICAL TRIALS

- **Null hypothesis:** This hypothesis, symbolized by H0, is a statement claiming that there is no difference between the experimental and population means. The alternative hypothesis (H1) is the opposite of the null hypothesis. Often in research, we need to be able to test for both the positive and adverse outcomes; therefore, a two-tailed hypothesis is chosen even though the expectation of the experiment is in a particular direction.
- **Significance level:** A level of significance termed the alpha value is determined before the study has begun. The alpha value is the likelihood that a difference as large or larger that occurred between the study groups could be determined by chance alone. The alpha level is established by those designing the study and becomes the level of statistical significance. The most typical alpha level is 0.05.
- **One-tail test:** A test to determine a difference in only one direction (eg, to determine if drug A is better than drug B)
- **Two-tail test:** A test to determine any difference between the variable (eg, if either drug A or drug B is superior to the other). It is usually considered that in a two-tailed test, more trust can be placed in the statistically significant results than with a one-tailed test. When in doubt, the two-tailed test is preferred.
- **Confidence interval (CI):** The range of values that is believed to contain the true value within a specific level of certainty.
- **Alpha error:** The rejection of the null hypothesis when it is, in fact, correct; also called a type I error.
- **Beta error:** Failure to reject the null hypothesis when it is, in fact, incorrect; also called a type II error.
- **Power:** The probability that a study will be able to correctly detect a true effect of a specific magnitude. The statistical power refers to the probability of finding a difference when one truly exists or how well the null hypothesis will be rejected. The power is usually specified beforehand in prospective studies. The values of 0.8 (80%) or 0.9 (90%) are typical. The higher the value, the less chance there is of a type II error. A 0.9 value means that a type II error would be avoided 90% of the time.

- **Risk:** The proportion of unaffected individuals who, on average, will contract the disease of interest over a specified period of time. Results of a trial are often expressed as absolute or relative risk reductions. The absolute difference is the actual difference between the units of the difference. In relative risk, the differences are the percentage change. Relative risk reductions often sound much more dramatic than do the absolute values. One must consider the prevalence of a disease when evaluating risk reductions. When there is a low prevalence of a disease process, small risk reductions become unimpressive and must be evaluated in terms of the benefits of a particular mode of therapy.
- **Incremental cost-effectiveness ratio:** The additional cost divided by the incremental benefit compared with an alternate strategy. A strategy was strongly dominated if it was more costly and less effective than another or cost effective if it had an incremental cost-effectiveness ratio of $50,000 to 100,000 per year of life gained relative to an alternate strategy.
- **Odds ratio (OR):** The ratio of the odds that an event will occur in one group compared with the odds that the event will occur in the other group. In an osteoporosis study, if 14 of 22 people who are thin, have fractures, the odds of having a fracture are 14 in 22 or 0.64. If 5 of the 33 nonthin people fracture bone, the odds are 5 in 33 or 0.15. The OR is 0.64 divided by 0.15 or 4.2, meaning that thin people are 4.2 times more likely to receive fractures. An OR of 1 means that both groups have a similar likelihood of having an event.
- **Overall survival (OS):** The interval from the completion of treatment to censoring or death from any cause.
- **Progression-free survival (PFS):** The interval from the date of randomization to the documentation of progression of the illness or death from any cause.
- **Actuarial (life table) survival:** This technique uses grouped information to estimate the survival curve. The data are grouped into fixed time periods (eg, months, years) that include the maximum follow-up. The survival curve is estimated as a continuous curve and gives an estimate of the proportions of a group of patients who will be alive at different times after the initial observation. The group includes patients with incomplete follow-up.
- **Chi square ($\chi 2$):** The primary statistical test used for studying the relationship between variables. This is a test used to compare proportions of categorical variables.
- **Cox proportional hazard regression analysis:** Cox regression analysis is a technique for assessing the association between variables and survival rate. The measure of risk provided for each variable is the risk ratio (RR). An RR of 1 means that the risk is the same for each participant. An RR greater than 1 indicates increased risk; a ratio less than 1 indicates less risk. A ratio of 5.4 means that the patients with a variable are 5.4 times more likely to have the outcome being studied. CIs can also be provided with RRs. This type of analysis is usually presented in a table.
- **Efficacy:** The possibility that an intervention will result in a change (eg, in vaccine trials).
- **Imputation:** In many analytical scenarios, a case is discarded if it is missing data relevant to the analysis. This may introduce a bias, decrease the power of the study, or alter the representativeness of the results. Imputation is the process of substituting missing data. There are numerous techniques to impute data.
- **Multivariate analysis:** A technique of analysis of data that factors many variables. A mathematical model is constructed that simultaneously determines the effect of one variable while evaluating the effect of other factors that may have an influence on the variable being tested. The two most common algorithms developed to accomplish this task are the step-up and step-down procedures. Variables are added to an initial small set or deleted from an initial large set while testing repeatedly to see which new factor makes a statistical contribution to the overall model.
- **Propensity score:** In studies in which randomization is not possible, investigators use this score to adjust for the bias due to confounding variables inherent in treatment selection for groups being compared (eg, in observational trials when the treatment of the participants is not random). Assignment to intervention does not occur by chance but depends on patient characteristics that can influence the effect of the intervention on the outcome. The propensity score is the probability that a patient would receive the treatment of interest based on the characteristics of the patient, clinician, and clinical environment. Several different techniques can be used to balance the groups being compared. The most common strategy is propensity score matching. Propensity score methods are usually better than matching on specific characteristics or stratification because it adjusts for confounding better than other strategies. This is a valuable approach when completion of a randomized trial is not feasible.
- **Receiver operator characteristics (ROCs):** These curves are the best way to demonstrate the relationships between sensitivity and specificity. The curves plot sensitivity (true-positive rate) against the false-positive rate (1 – Specificity) (Fig. 22.2). The closer the curve is to the upper lefthand corner, the more accurate it is because the true-positive rate is closer to 1 and the false-positive rate is closer to 0. Along any particular ROC curve one can observe the impact of compromising the true-positive and false-positive rates. As the requirement that a test has a high true-positive rate increases, the false-positive rate will also increase. The closer the curve is to the 45-degree diagonal of the ROC area under the curve, the less accurate the test (see Fig. 22.2).
- **Sensitivity analysis:** Modeling is a tool that permits the incorporation of data from different sources to predict outcomes that may be likely. This tool allows for various interventions and numerous scenarios. Interpretation of the findings depends on the confidence the operator has in various factors of the model. Sensitivity analysis involves examination of the variation in the outcome as the variables change.
- **One-way sensitivity analysis:** This is the simplest form of sensitivity analysis in which the effectiveness of only one

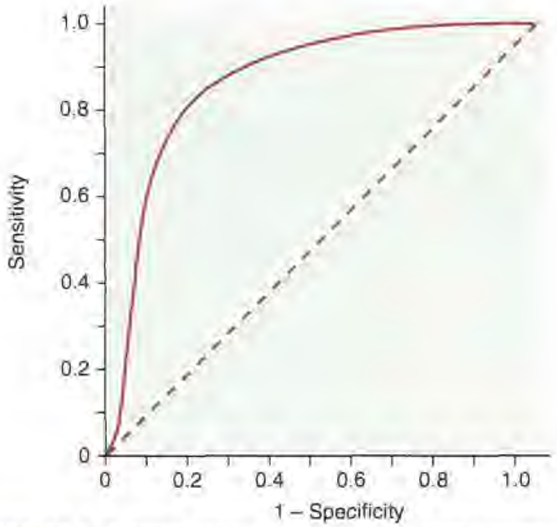

FIGURE 22.2 A hypothetical example of a receiver operating characteristic curve. The *solid line* represents the performance of the diagnostic test of interest; the *dashed diagonal line* serves as a reference of a test with no diagnostic value. (From Greenberg RS, Daniels SR, Flanders WD, et al: *Medical Epidemiology*, 3rd ed. Lange Medical Books/McGraw-Hill, 2001 Reproduced by permission of The McGraw-Hill Companies.)

variable in the model is analyzed to assess the range of impact of that variable on the outcome.

- **Univariate analysis:** Analyses may be univariate or multivariate because they examine one or more variables at a time, respectively.

TYPES OF CLINICAL TRIALS

Clinical trials are experiments in which the investigator intervenes rather than observes and is the best test of a cause-and-effect relationship. A properly conducted experiment requires that when the intervention is applied to one group, there is a control group or some other suitable standard by which participants of the clinical experiment or their guardians must give informed consent. The gold standard of clinical trials is the randomized experiment. With randomization, each participant has an equal chance of being in either of the arms of the trials. Randomization is important because it equalizes baseline characteristics of the participants so that the comparison of the treatments is fair. If randomization is not feasible, possible nonrandom standards of comparison must include patients similar to the treated group. Randomization is the current norm for demonstrating efficacy and safety of investigational methods. The advantages of randomization are numerous:

- Decreases investigator's bias in assigning patients to treatment groups
- Permits certain statistical methods to be used in the resulting data
- Allows for blinding of the patient and investigator
- Is the current norm for demonstrating efficacy and safety of investigational medicines

BOX 22.2 Types of Clinical Trials

Single-patient clinical trials
Multicenter trials
National clinical trials
Continuation trials
Compassionate plea trials
Pharmacoeconomic trials
Trials to evaluate medical devices
Pharmacokinetic trials

Unacceptable methods of randomization include the following:

- Alternate assignments
- Alternate day assignments
- Birthday assignments
- Coin tosses
- Initials of a patient

Single-patient clinical trials are indicated only in specific situations. They are generally used to evaluate rare diseases when other types of trials are inappropriate or when only a small percentage of patients respond to a specific treatment. Single-patient clinical trials are useful to determine the response of a particular patient is a result of placebo or if an adverse reaction is related to a specific medication. The disease should be chronic, and the disease severity must be stable during the clinical trial duration. It should be expected that the effect of the treatment should be measurable in a short time, and the effect should be rapidly reversible after the treatment has stopped. The investigator and patient should be blinded, and the patient's condition should return preexisting baselines between treatment legs.

Multicenter trials are advantageous because they offer more rapid patient accrual and allow for greater protocol complexity. Multicenter trials reduce the opportunity for an individual's bias to influence the conduct of the trial; they increase the likelihood for the inclusion of a more representative study population and facilitate a higher standard for data processing and analysis. Disadvantages of multicenter trials are the administrative considerations that underlie the management and administrative arrangements (eg, institutional review board, ethics committees). Considerations must be delineated for criteria for patient enrollment, diagnostic classification, and assessment of treatment outcome. These trials are inherently more costly (Box 22.2).

EVALUATION OF CLINICAL TRIALS

Many factors must be considered when evaluating a clinical trial. The most important is the clinical trial objective or aim. Whether the objectives of the trial are adequately assessed depends on the presence and extent of bias and confounding factors. Bias is a nonrandom error in a study that can alter the outcome. Types of bias to consider when evaluating a manuscript are listed in Table 22.2.

TABLE 22.2 Bias and Confounding Factors: Examination of the Literature in the Field

- Specifying and selecting the clinical trial sample
  - Popularity bias
  - Referral filter bias
  - Diagnostic or access bias
  - Wrong sample size
  - Migrator, nonrespondent, or volunteer bias
- Executing the exposure
- Contamination, withdrawal, or compliance/therapeutic bias
- Information bias
- Observer bias
- Interviewer bias
- Use of nonvalidated instruments
- Active control bias
- Analyzing the data
  - Post hoc significance bias
  - Fishing expeditions
- Interpreting the analysis
- Publishing the results

Specifying the sample size or number of participants in the study needed to detect a difference or an effect of a given magnitude depends on many variables. The most important is the magnitude of the effect desired or expected. Other important considerations are the desired probability of the study to identify the correct outcome (power), the variability of the variables being analyzed, the number of parts of the clinical trial, the magnitude of the placebo effect, and the number of dependent parts of the clinical trials. When determining the sample size, one must consider if the size of the treatment groups will be equal or nonequal (eg, 2:1 ratio). **An advantage of using groups of unequal size is that more information will be gained about patient responses in the larger arm. A disadvantage is the loss in study power; however, this detraction is not usually substantial if the ratios are kept under 3:1.**

Placebo Treatment Groups

Placebo treatment groups control for the psychological aspects of being in a treatment trial. They also control for adverse events being attributed to a medicine when they result from spontaneous changes in the disease or from other causes and allow a stronger interpretation of the data. Placebo treatment groups are considered ethical if the following occur:

- No standard treatment exists.
- The standard treatment has been proven ineffective.
- Standard treatment is inappropriate for the particular clinical trial.
- Placebo has been reported to be effective in treating the condition.
- The disease is mild and lack of treatment is not considered to be medically important.
- The disease process is characterized by frequent spontaneous exacerbations and remissions.

Controls Used in Clinical Trials

Control groups in clinical trials may be obtained by many different methods. Randomized control groups are the most traditional and accepted and only chance should determine who enters any of the study arms. Nonrandom control groups may also be used. Participants in these nonrandom control groups should have similar characteristics to those of the "treatment arm" and may include historical data obtained on the same patients on no therapy, the same therapy, or different therapy. Participants in the control arm may be assigned to a placebo, an active medication, or concurrent use of nontreatment; use a different dose of the same medication; or receive usual care.

Dropouts from clinical trials are inevitable. The simplest reasons may be that the participants declined to participate after enrollment or that the clinical course during the trial required a change in therapy. Whatever the reason for noncompliance or dropout, these participants should be followed because it is essential to analyze the outcomes of the groups as intent to treat. Inclusion of these data provides a conservative estimate of the differences in treatment.

Studies of Therapy

There are many different types of clinical trials; in general, they are categorized into categories or phases. Phase I trials are usually to screen the safety of the intervention or drug. These trials can be inclusive of multiple doses of a new medicine or evaluation of an old medicine in a new therapeutic area. These trials usually consist of 10 to 100 participants.

Phase II trials clarify and establish the protocol and elucidate the experimental conditions that will allow the most important phase of the trial to give a definitive result. These trials are valuable because they establish protocols and the experimental conditions that will allow the final phase of the trial to give a definitive result. They allow for the following:

- The evaluation of a variable related to the clinical pharmacology of a medicine
- Development of clinical experience by research personnel under open-label conditions before initiation of a double-blind trial

Aims of phase II trials are to assess how many people should be included in the final phase of testing, determine the endpoints of the trial, and provide preliminary estimates of effective dose and duration of treatment.

Phase III trials are for comparison to standard therapy or placebo if ethically justifiable. These trials are more commonly randomized and are regarded as the best way to obtain unbiased data.

Blinding

Blind refers to the lack of knowledge of the investigational agent by the patients, investigators, ancillary personnel, data review committees, and statisticians. Blinding is used to decrease the biases that may occur during a clinical trial. An open-label trial indicates that no blind is used. Examples of open-label trials are as follows:

- Pilot trials
- Case studies in life-threatening situations

- Unusual studies in which definitive data may be obtained (eg, coma patients)
- Clinical trials in which ethical considerations do not permit blinding

In single-blind clinical trials, either the patient or investigator is unaware of the treatment received. Single-blind trials provide a degree of control when a double-blind trial is impossible or impractical and provides a degree of assurance of the data's validity compared with open-label trials. In double-blind trials, neither the investigator nor the patient is aware of what treatment the patient is receiving. This allows for strong data interpretation if all other aspects of the trial were properly designed and conducted, the blind remained intact, the protocol was not seriously breached, the power of the trial was adequate, and the patients were compliant. Triple-blind trials are situations in which anyone who interacts with either the patient of physician is blinded. These studies allow for the strongest interpretation of data if the conditions can be met.

If blinding is to be used, then the study should be designed so that it is very difficult to break the blind. Unblinding may occur based on any of the following:

- Adverse reactions
- Lack of efficacy
- Efficacy
- Changes in laboratory values
- Errors in labeling
- Comments from unblinded study personnel
- Information presented in correspondence or reports
- Intentionally looking for clues (Box 22.3)

BOX 22.3 Types of Blinds

Open label
Single blind
Double blind
Full double blind: keeping blind everyone who interacts with the patient
Full triple blind: keeping blind anyone who interacts with the patients and the investigators

When to Stop a Clinical Trial

The decision to stop a clinical trial has many important ramifications. The ethical dilemmas include the needs of the next eligible patient insomuch that a participant should never be randomly assigned to an established inferior treatment. This must be balanced by the collective needs of society that terminating a trial will still result in the correct policy for the future and the need for sufficient data to change clinical practice for the better.

Early termination of a trial has its disadvantages. If the trial is stopped after recruitment of a small number of participants, the results may lack credibility. The assumed treatment difference may be the result of chance and a false-positive result. The early stopping of trials can result in imprecision and wide CIs for treatment effect. Finally, the treatment recommendation that results from stopping a trial early may be unduly enthusiastic.

Statistical stopping guidelines should be determined before the clinical trial begins. A sufficiently small *P* value for treatment difference on a trial's primary endpoint can be a guideline for when it is ethically desirable to stop a trial. It is most acceptable to have a limited number of preplanned interim analyses. Multiple repeated looks at the data can guard against the risk of a false-positive result.

For the bibliography list, log onto www.expertconsult.com ⟨http://www.expertconsult.com⟩.

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Exhibit 121

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF NEW JERSEY

----------X

IN RE: JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES, AND PRODUCTS LIABILITY LITIGATION

MDL No.: 16-2738 (FLW)(LHG)

----------X

ORAL AND VIDEOTAPED DEPOSITION OF DANIEL L. CLARKE-PEARSON, M.D.

MONDAY, FEBRUARY 4, 2019

9:03 A.M.

Taken by the Defendants
at The Carolina Inn
211 Pittsboro Street
Chapel Hill, North Carolina 27516

- - -

Reported by Sophie Brock, RPR, RMR, RDR, CRR

- - -

GOLKOW LITIGATION SERVICES
877.370.3377 ph | 917.591.5672 fax
deps@golkow.com

A P P E A R A N C E S

ON BEHALF OF THE PLAINTIFFS:
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P R O C E E D I N G S

THE VIDEOGRAPHER: We are now on record. Today's date is February 4, 2019, and the time is approximately 9:03 a.m.

This is the videotaped deposition of Dr. Daniel Clarke-Pearson. It's being taken in regards to the Talcum Powder Litigation, MDL No. 2738.

Would counsel please now introduce themselves for the record, and then our court reporter will swear in the witness.

MS. O'DELL: Leigh O'Dell from Beasley Allen, on behalf of the plaintiffs.

MS. THOMPSON: Margaret Thompson, Beasley Allen, on behalf of the plaintiffs.

MS. BROWN: Paula Brown from Blood, Hurst & O'Reardon, on behalf of the plaintiffs.

MR. ZELLERS: Michael Zellers, on behalf of the Johnson & Johnson defendants.

MS. BRENNAN: Jessica Brennan, on behalf of the Johnson & Johnson defendants.

MR. BILLINGS-KANG: James Billings-Kang, Seyfarth Shaw, on behalf of Personal Care Products Council.

MS. BOCKUS: Jane Bockus, on behalf of Imerys.

MS. MESEHA: Maryam Meseha, on behalf of Imerys.

MR. MIZGALA: James Mizgala, on behalf of PTI.

Whereupon,

DANIEL L. CLARKE-PEARSON, MD,

having first been duly sworn/affirmed, was examined and testified as follows:

EXAMINATION BY COUNSEL FOR THE JOHNSON & JOHNSON DEFENDANTS

BY MR. ZELLERS:

Q. Can you state your name, please.

A. Yes. Daniel Lyle Clarke-Pearson.

Q. Dr. Clarke-Pearson, we're here to take your deposition in the talcum powder MDL litigation. You're aware of that?

A. Yes, sir.

Q. You've given a number of depositions in the past; is that right?

A. I have.

Q. You are familiar with the rules that we're going to follow here today?

A. Yes.

Q. If I ask you a question or if any counsel asks you a question that you don't understand, tell us

you don't understand and we'll repeat or rephrase the question so it's clear to you.

Can you do that?

A. Yes, sir.

Q. If you answer a question, we're going to assume that you understood it. Is that fair?

A. Fair.

MS. O'DELL: Objection.

BY MR. ZELLERS:

Q. As we go along, only one of us can speak at a time. So please try to let me finish my question before you answer. I will try to allow you to finish your answer so that we can get the best record possible.

Is that agreeable?

A. Agreeable.

Q. All right. You are following this, apparently, on the realtime; is that right?

A. Yes.

Q. Is that going to be distracting to you?

A. It might be.

Q. All right. Well, have you ever done that before in a deposition?

A. No, sir.

Q. Well, if it becomes distracting, then we'll

deal with it.

You are here pursuant to a notice of deposition. We've marked the notice of deposition as Exhibit 1.

(Exhibit No. 1 was marked for identification.)

BY MR. ZELLERS:

Q. Can you take a look at that and let us know if you've seen that before?

MS. O'DELL: I would just reassert that the objections to certain document requests in the notice, I think those were previously served.

MR. ZELLERS: Yes, we did receive the objections of plaintiffs.

THE WITNESS: Yes, I've seen this.

BY MR. ZELLERS:

Q. If you go to -- beginning on page 3, there are a number of documents that are requested be produced here today.

Have you either brought with you here today or supplied to counsel for plaintiffs all of the documents and materials in your possession that are requested in the deposition notice?

MS. O'DELL: To the degree that they are not objectionable --

MR. ZELLERS: No. My question goes,

you know, across the board. If there is a document that he has in his possession that may be objectionable, then he can tell us what it is and you can assert your objection.

MS. O'DELL: Well, you asked if he had brought them here, and Dr. Clarke-Pearson has only brought materials subject to requests that are not objectionable, which include the materials listed in his materials-considered list that are in the binders behind me on the table.

They also include binders of cited materials, his report, invoices, and the cases in which he has provided testimony within the last five years. I think he has a copy of his report in front of him.

Those are the materials we view to be nonobjectionable, and those are what Dr. Clarke-Pearson has brought with him today.

MR. ZELLERS: Okay. Ms. O'Dell, as we -- I would appreciate it if you let the witness answer the questions. I do appreciate the clarification. But, as we go along today, if you'll do your best, you know, to follow the rules. I mean, the both of us need to follow in terms of objections. I'd appreciate it.

MS. O'DELL: Well, certainly, I'm going to follow the rules today, but it's because of the objections asserted and because it's unclear to what degree Dr. Clarke-Pearson is familiar with all the requests and all the objections, then that was just a difficult question for him -- maybe an unfair question for him. And so I have responded in keeping with our previously served objections.

MR. ZELLERS: I don't think asking him if he's gone through the request for production of documents and can identify for us any documents that are in your possession that are responsive that you've not brought here today, I don't think that is a difficult question. But let's have Dr. Clarke-Pearson answer it.

THE WITNESS: I don't think I've brought any of these documents here today. Counsel has some of them, like my curriculum vitae.

BY MR. ZELLERS:

Q. My question, I guess, goes to -- so that we can identify whether there's anything at all for us that we need to fight about should be produced.

Are there documents that are responsive to the notice of deposition that are not being produced here today, to your knowledge, that originated from

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you and are in your possession?
A. I think let's just walk through the list, then. I don't have a CV in my possession, but counsel does --
Q. And, Doctor, to shortcut this, I don't need to go through and ask you, you know, what documents are being produced.
Are you aware of documents that are called for in the notice of deposition that are not being produced today?
A. I don't -- I would have to go through this list. I don't have any documents with me aside from what you've just described.
Q. So you've reviewed the notice of deposition in preparation for today; correct?
A. Yes.
Q. You knew that was important; correct?
A. Yes.
Q. And yet you're unable to tell us whether or not there are documents that are in your possession that are called for in the notice of deposition that you are not producing today; is that right?
MS. O'DELL: Objection. That's not correct, but --
MR. ZELLERS: Well, he can answer.

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MS. O'DELL: I've made my objection --
MR. ZELLERS: Understood.
MS. O'DELL: -- which I'm perfectly entitled to do that, as you know.
MR. ZELLERS: You certainly are. You certainly are.
MS. O'DELL: So, Dr. Clarke-Pearson, just answer to the best of your knowledge, and, of course, there are objections that have been asserted; and to the degree you're not familiar with those details, then counsel and I can sort that out later.
THE WITNESS: So documents -- I do not have any of these documents in my possession. For example, I thought I saw -- passed you a document showing my billing and collections to date. Isn't that right on top?
BY MR. ZELLERS:
Q. My question was are you aware, as you sit here right now, of any documents that you have that are responsive to the notice of deposition that are not in the large pile of materials that we have here today?
A. I'm not aware of any.
Q. All right. Ms. O'Dell produced for us or provided to me two documents prior to the deposition

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and then has advised me that you have reviewed a number of additional materials since you prepared your report. So I'd like to go through those now, if we can.
Notice of deposition, Exhibit 2, is a copy, it appears, of your invoices in this matter. Is that right?
(Exhibit No. 2 was marked for identification.)
THE WITNESS: Yes, sir.
BY MR. ZELLERS:
Q. You have spent a total of 20 hours working on this matter since being retained back in April of 2017; is that right?
MS. O'DELL: Object to the form.
THE WITNESS: Up until the preparation of -- and submission of my report, I spent 20 hours.
BY MR. ZELLERS:
Q. All right. You prepared your report, you edited your report, and you submitted your report on November 4th of 2018; is that right?
A. I believe it was -- I submitted it, but I think it was November 16th, 2018.
Q. Did you bill any time or spend any time on the MDL talcum powder litigation between November 4th of 2018 and the end of the year,

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December 31st of 2018?
A. Yes.
Q. How much additional time did you spend during that time?
A. I don't know exactly. I'd have to go back to several notes that I have on records and papers and that sort of thing. I would say between November 4th and today, it's been about 60 hours.
Q. 60 additional hours?
A. Yes, sir.
Q. So you spent 20 hours talking with counsel, doing whatever research and analysis you needed to do, and writing your report; is that right?
A. Yes.
Q. You have spent an additional 60 hours since that time; is that right?
A. Yes.
Q. If your invoice is dated January 4th of 2019, Exhibit 2, why does none of that time appear on your invoice?
A. Because my accounting office turned this over on January 4th. I submitted -- I submitted this invoice to my business manager, and this is when it was submitted from our office.
Q. I guess I don't understand. You tell me that

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you have worked a considerable amount of time between November 4th of 2018 and the end of 2018; correct?
A. Yes.
Q. Why is that time and those hours not reflected on your invoice which is dated January 4th of 2019?
A. Because I hadn't submitted the request for my business manager to submit the invoice to the attorneys.
Q. Why did you cut off your time entry as of November 4th, 2018?
MS. O'DELL: Object to the form.
THE WITNESS: I think there was a gap. I can't tell you when I picked up again after November 4th, after I did the report. There was a time when I wasn't actively involved reading, preparing.
BY MR. ZELLERS:
Q. Do you keep track of the time that you spend doing activities as an expert witness in the MDL talcum powder litigation?
A. Yes.
Q. And do you keep that on a regular, systematic basis?
A. Not so much.

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Q. Were you first retained back in April of 2017 by Ms. O'Dell and by Ms. Thompson?
A. Yes, I believe so.
Q. Had you known Ms. O'Dell or any attorneys from her office, the Beasley Allen office, prior to being contacted in this litigation?
A. I had not known Ms. O'Dell. I knew Dr. Thompson.
Q. How did you know Dr. Thompson?
A. Dr. Thompson and I were residents at Duke University Medical Center. I was a few years ahead of her, but we were in the residency training program. And then I began my fellowship and gynecologic oncology at Duke, and I believe Dr. Thompson was still a resident during part of that time.
Q. Did you make -- maintain contact with Dr. Thompson over the years?
A. Off and on. Probably on average about once a year at an alumni meeting that we attended, although neither one of us attended every year, but...
Q. These were alumni meetings at Duke University; is that right?
A. With regard to the obstetrical and gynecological department.
Q. Other contacts that you had with

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Ms. O'Dell -- strike that -- with Dr. Thompson over the years?
A. I believe she probably called me somewhere before April 17th when I was retained and described work that was ongoing with talcum powder. So we had a conversation. I didn't bill for that.
Q. You knew Dr. Thompson socially before being retained; is this correct?
A. Yes.
Q. Other than --
A. And -- excuse me. And professionally.
Q. Socially and professionally.
What professional interaction did you have with Dr. Thompson since the time that you were a resident and a fellow at Duke University?
A. Okay. So since that time -- I mean, throughout her residency, we were professionally involved with training and taking care of patients. Subsequent to her completing her residency, I've not had any professional interaction with her per se.
Q. Were you socially involved with Dr. Thompson while the two of you were at Duke?
A. No.
Q. You might go to events and see one another, but in terms of any relationship between the two of

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you, there was none; is that fair?
A. I guess you'll have to define "relationship" for me.
Q. Well, I was trying to make it easy.
Did you socialize with other persons in the internship and residency programs while you were at Duke?
A. Yes. And faculty and spouses, yes.
Q. And Dr. Thompson was one of those persons; is that right?
A. Yes, sir.
Q. Do you know Dr. Thompson's husband or former husband?
A. I did not.
Q. All right. Your contact was solely with Dr. Thompson; is that right?
A. Yes.
Q. Over the years, prior to being retained by Dr. Thompson in this litigation, did you review any medicolegal matters for her?
A. No, sir.
Q. Were you asked to review any medicolegal matters for her?
A. You just asked that question, I think.
Q. No --

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A. Did I misunderstand?
Q. Well, and at least what I had hoped was the distinction is that I had asked you if you had reviewed any matters, and then the second question was whether or not Dr. Thompson had requested that you review any medicolegal matters for her.
A. Okay. So it's a two-part question. I did not review any matters, and Dr. Thompson hadn't requested me to review any medicolegal matters.
Q. When -- well, strike that.
What did Dr. Thompson ask you to do with respect to the MDL talcum powder litigation?
A. At the time of the conference call with Ms. O'Dell and Dr. Thompson, I was asked to evaluate and offer my opinion regarding talcum powder and whether it was causative to the occurrence of ovarian cancer in women who use talcum powder on their perineum.
Q. Were you asked to research or answer any other question other than that?
A. So in my report, I think I make it clearer than what I just described. So "Can the use of talcum powder in the perineal area cause epithelial ovarian cancer?" and also, "If so, what biologic mechanism did this -- by which did this occur?" were the two key

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questions I was asked to form an opinion on.
Q. You mentioned that you did speak with Dr. Thompson prior to the conversation with Ms. O'Dell and Dr. Thompson.
What, at that time, did Dr. Thompson tell you about the litigation?
A. I don't recall details. It was that she was working on cases that had to do with talcum powder and ovarian cancer.
Q. Do you recall any other background that you were provided?
A. Not at that time.
Q. Did you understand that Dr. Thompson was representing the plaintiffs in this matter, along with a number of other attorneys?
A. Yes.
Q. Prior to being contacted by Dr. Thompson and by Ms. O'Dell, had you formed opinions in terms of whether or not talcum powder was causally related to ovarian cancer for women who used it in the perineal region?
A. So that's an interesting question, because it goes back to my training. And throughout the years, since 1975, when I began my residency training, the conversation in the gynecologic community and the

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GYN oncology community has been one of could talcum powder be associated with the occurrence of ovarian cancer?
And, in fact, I think, in the early '70s, we believed it did; and then I was told as a trainee that talcum powder previously had had asbestos in it, and then we were told it was taken out. So that was very reassuring.
Yet periodically over the years, papers came out -- case-control studies, cohort studies -- off and on that continued to raise the question.
So the question has been in my mind. And, really, it wasn't until I really started thinking about this and gathered up all the literature that it became clear to me, and I formed my opinion.
Q. That was my question. When did you form your opinion that talcum powder is causally related to ovarian cancer when used by women in the genital area?
A. Well, some -- I'm not sure there was a particular day when the light bulb went off. I think in the process of digging into this issue in more detail and putting together all the case-control trials that had come out over a period of time and the meta-analysis that had come out over a period of time that kept raising questions, when I started to put

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that all together, it became clear to me that, in my opinion, talcum powder causes ovarian cancer.
Q. That was sometime after you were contacted and retained in this matter back in April of 2017 as an expert for the plaintiffs; correct?
A. It was the request to provide opinions and to develop an opinion, and I -- yes.
Q. All right. Do you agree that the medical community as a whole has not reached a consensus that talcum powder causes ovarian cancer?
MS. O'DELL: Object to the form. Excuse me.
THE WITNESS: I think we're at a tipping point in that question.
BY MR. ZELLERS:
Q. Can you answer that question?
A. Well, I think you would have to define "the medical community" for me.
Q. Well, let's be more specific.
Has the gynecologic oncologist medical community reached a consensus that talcum powder causes ovarian cancer?
A. As best I know, not at this time.
Q. All right. You also -- Ms. O'Dell provided me with an updated list of your testimony; is that

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right?
MR. ZELLERS: We'll mark that as Exhibit 3.
(Exhibit No. 3 was marked for identification.)
THE WITNESS: Yes, sir.
BY MR. ZELLERS:
Q. The testimony that you provided back in November of 2017 -- strike that -- November of 2018, when you submitted your report, Exhibit C -- we'll mark that as Deposition Exhibit 4 --
(Exhibit No. 4 was marked for identification.)
Q. -- contained just one listing of testimony; is that right?
A. Yes.
Q. What has changed since you prepared your report in November of 2018 and today with respect to deposition and trial testimony that you have provided?
A. I believe simply an oversight on my part.
Q. The oversight was not listing at least two of the matters that you had testified in in the past five years as of November of 2018; is that right?
A. Yes, sir.
Q. The Edmonson matter that you testified in December of 2014, was that a medical malpractice action?

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A. Yes, it was a malpractice action.
Q. And September 1st of 2015, the Rappaport matter, that was a physician who was losing his or her privileges?
A. He was being fired from his practice.
Q. The Pizzirusso case or matter that you provided testimony in March of 2015, what was that?
A. That was a medical malpractice case in Brooklyn, New York.
Q. January of 2019, Paduda, what type of matter was that?
A. This was -- I need to make sure I've got the two straight here. Yes, it's a medical malpractice case.
Q. And then, finally, you were deposed on January 22nd of 2009 in a matter called Cutsinger. What type of matter was that?
A. It was 2019.
MS. O'DELL: '19.
MR. ZELLERS: Thank you, Counsel.
BY MR. ZELLERS:
Q. January 22nd of 2019.
A. This is a product liability suit.
Q. Involving what product?
A. A morcellator manufactured by Gyrus.

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BY MR. ZELLERS:
Q. The medical malpractice cases that you have listed -- Edmonson, Pizzirusso, and Paduda -- were you serving as an expert for plaintiff or defense in those cases?
A. In all three of those cases, for the defense.
Q. Over the years, you have done a lot of testifying in medical malpractice cases. Is that fair?
MS. O'DELL: Object to the form.
THE WITNESS: I don't know how you define "a lot."
BY MR. ZELLERS:
Q. Have you given -- at least up until 2005 or so, did you give about three depositions a year in medical malpractice cases?
A. Probably three or more. Three to six, maybe.
Q. Since 2005, you've cut back some in terms of your medicolegal work; is that right?
A. Yes.
Q. Is it accurate to say that, over the years, you've testified about 50 percent for plaintiff and about 50 percent for defendants in litigation matters?
A. Yes.
Q. Is the only product liability matter that you

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have testified in, other than the MDL talcum powder litigation, the morcellator deposition that you gave earlier in -- this year, in January?
A. Yes, sir.
Q. Ms. O'Dell advised us at the start of the deposition that, in addition to the materials that you cite in your report and in your additional materials list, that you have now reviewed a number of additional materials prior to today; is that right?
A. Yes.
Q. Do those additional materials that you have reviewed change in any respect the opinions that you have set forth in your report?
A. They reinforce and enhance or support my opinion.
Q. As we go through today, I may refer to talc, I may refer to talcum powder, I may refer to talc products or to baby powder or to Shower to Shower. I intend, when I use those terms, to be referring to the baby powder product manufactured by Johnson & Johnson Consumer Products Inc. and the Shower to Shower product formerly manufactured by Johnson & Johnson Consumer Products Inc.
Do you understand that?
A. I understand.

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Q. Your report which was provided to us, we will mark as Deposition Exhibit 5.
(Exhibit No. 5 was marked for identification.)
BY MR. ZELLERS:
Q. Can you just take a quick look at that and confirm for us that that is Deposition Exhibit 5?
A. It is.
Q. Your report, which we have marked as Deposition Exhibit 5, does that contain all of the opinions that you intend to offer at any trial or hearing in this matter?
A. I believe so, yes.
Q. Does your report identify everything that you are relying on in forming your opinions in this matter?
MS. O'DELL: Object to the form.
THE WITNESS: Obviously, we just talked about some additional information -- materials that I've reviewed since writing that report, so they would be included in my opinion.
BY MR. ZELLERS:
Q. We'll go through in a moment the additional materials that you have reviewed.
If we look at your report and if we look at the additional materials that you have reviewed in

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preparation for the deposition, does that include all of the materials that you are relying on in forming your opinion?
A. To be clear, you're saying what I have included in my report plus my additional materials, that's what I relied on?
Q. Yes.
Is that correct?
A. Yes.
Q. Is your report accurate?
A. Yes.
Q. Is your report complete?
A. I believe it is.
Q. Let's try to quickly go through, if we can, the additional materials that you have reviewed since you prepared your report, Exhibit 5.
Ms. O'Dell stated that you have reviewed the Health Canada risk assessment; is that right?
A. Yes.
Q. You have reviewed the Taher, T-A-H-E-R, 2018 publication; is that right?
A. Yes.
Q. You have reviewed the 2019 Saed paper?
A. Yes.
Q. You have reviewed the Longo supplemental

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report?
A. Yes.
Q. You've reviewed a chapter of a book by Creasman that was authored by Dr. Brewster; is that right?
A. That's correct.
Q. Is there anything else that you have reviewed and are relying on in preparation for your deposition today and in providing us with your opinions?
A. So all these references here (indicating), I've reviewed. I believe they're listed as part of an exhibit.
Q. And let's, you know, be as systematic as we can be.
Your report, Exhibit 5, has a list of references; is that right?
A. Yes.
Q. What do you intend -- or what is the meaning of the references that appear as pages 11 through 14 in your report?
A. Those references support what I quote -- not quotes, but facts that are in my report. They don't include everything that I used in my consideration of coming to my opinion.
Q. Deposition Exhibit 6 is Exhibit B to your

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report.
(Exhibit No. 6 was marked for identification.)
BY MR. ZELLERS:
Q. Is that correct?
Is Deposition Exhibit B a listing of additional materials considered?
A. Yes, it is.
Q. Did you actually read and consider all of the materials that are cited as Exhibit B to your report?
A. I would say I did not read every word of every paper. I reviewed them, many times reading the abstract.
Q. Did you read at least the abstract of each of the references contained as Exhibit B to your report, going from page 1 through page 28?
A. I believe so.
Q. Exhibit B is meant to be materials that you considered but are not directly relying on in formulating your opinions; is that fair?
MS. O'DELL: Object to the form.
THE WITNESS: That's fair.
BY MR. ZELLERS:
Q. In addition to the references that are attached to your report, Exhibit 5 to the deposition, and Exhibit B, which we've marked as Exhibit 6 to the

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deposition, are there any other materials that you have reviewed and relied upon in formulating the opinions you're going to give today other than the additional materials that we discussed a moment ago?
A. No.
Q. Are there any additional materials that you have reviewed and relied upon since the time of your report other than the materials that have been identified by Ms. O'Dell?
A. No.
Q. Did you bring those additional materials with you in the folders that you have in front of you?
A. Some of them. I have the Longo updated report, for example.
Q. All right. I'd like to just mark, so that we have a record of what it is you have reviewed, to the extent there's any ambiguity in the record. And, for example, I'm looking at --
MS. O'DELL: Mike, excuse me. Can I just mention one thing?
MR. ZELLERS: Yes.
MS. O'DELL: Because when you were going through your list, I had mentioned before an UpToDate reference. It's in the stack I think you have in your hand. But you didn't mention that in

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your sort of questions to Dr. Clarke-Pearson. So I don't want there to be a misrepresentation --
MR. ZELLERS: Understood.
MS. O'DELL: -- on the -- I didn't mean it that way. I didn't want there to be a misunderstanding on the record.
MR. ZELLERS: I do understand. I appreciate the clarification.
BY MR. ZELLERS:
Q. What I had been given was a clip with the Brewster chapter from the Creasman textbook. But in addition to what was on top, there is an UpToDate official reprint that states at the top "Evidence-based medicine," and then it lists several authors, the first of which is Arthur T. Evans; is that correct?
A. Yes.
Q. That's an additional set of materials that you have reviewed and relied upon?
A. Yes.
Q. Also in the stack, and something that I did not mention earlier, is "Emerging Themes in Epidemiology, Analytical Perspective." First author is Fedak. And this appears to be a 2015 publication.
Is that also something that you reviewed and

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you relied upon?
A. Yes, sir.
Q. We'll mark the Brewster chapter as Exhibit 7.
(Exhibit No. 7 was marked for identification.)
MR. ZELLERS: We will mark the UpToDate reprint as Exhibit 8.
(Exhibit No. 8 was marked for identification.)
MR. ZELLERS: We will mark the Emerging Themes in Epidemiology, 2015, Fedak, as Exhibit 9.
(Exhibit No. 9 was marked for identification.)
BY MR. ZELLERS:
Q. I'll return these to you, Doctor.
Can you show me or provide to me whatever folders you have brought. I don't need the binders, but just whatever additional materials you have brought with you.
(Document was handed to counsel.)
BY MR. ZELLERS:
Q. And then it looks like you have IARC monographs; is that right?
A. Yes.
Q. Are those IARC monographs that you have brought with you, is that something that's either on your reference list or your reliance list?
A. I believe it is.

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Q. Can you just tell us the title of the IARC monograph that you have brought with you?
A. "IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 93, Carbon Black, Titanium Dioxide, and Talc," dated 2010.
Q. The next set of materials, I'll mark these collectively as Exhibit 10 so we can keep them in the same order that you have brought them with you.
(Exhibit No. 10 was marked for identification.)
BY MR. ZELLERS:
Q. Exhibit 10, the first page is a listing of handwritten notes. Can you read just the first line to us.
A. "Exposure IARC 100C page 232."
Q. What does that refer to?
A. I put these together, if I can explain, so that we might facilitate this discussion and be able to find documents a little bit more quickly.
Q. What discussion does Exhibit 10 relate to?
A. Could I see the front of the folder, please?
Q. Sure.
A. It has to do with asbestos and ovarian cancer.
Q. I will re-mark Deposition Exhibit 10. Instead of putting the sticker on your page of

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handwritten notes, I'll put it on the outside of the folder, which are your references on asbestos and ovarian cancer; is that right?

MS. O'DELL: Object to the form.

THE WITNESS: They are some of my references.

BY MR. ZELLERS:

Q. These are the references, though, that you chose to bring with you today to be prepared to answer questions that the lawyers may ask?

MS. O'DELL: Object to the form. He brought other references as well.

THE WITNESS: All of these references here are -- also could support the question in that folder about asbestos and ovarian cancer.

BY MR. ZELLERS:

Q. Who prepared the folder "Asbestos on Ovarian Cancer"?

A. I did.

Q. Whose notes are the first page of this folder?

A. That's mine.

Q. Who chose to include and to write down the references that you did on this piece of paper?

A. I did.

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Q. The other exhibits that you have today, the exhibits that we marked, was it -- Exhibit 9, is that the Brewster chapter?

A. Exhibit 7 is the Brewster chapter.

Q. Okay, Exhibit 7. Who provided those materials to you?

A. This is from a textbook in my office.

Q. Okay. Did you obtain that -- you know, that information?

A. I'm not quite sure -- so I wrote a chapter for this textbook myself on surgical complications. It's a textbook that's in my office. This particular document, if you will, or reprint from that chapter, I'm not sure if I produced it or counsel did.

Q. Well, it's clear at the bottom that it was produced by counsel; correct?

A. Okay.

Q. There's a notation that Dr. Thompson downloaded that reference back in January of this year; is that right?

A. I see that, yes.

Q. Are many of the materials that you've looked at, including those on your reference list, your additional materials-considered list, materials that were provided to you by counsel for the plaintiffs?

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MS. O'DELL: Object to the form.

THE WITNESS: Many of them were reprints that I created, and some were given to me by counsel.

BY MR. ZELLERS:

Q. Are you able -- if we went through your list of references that are attached to your report, Exhibit 5, are you able to tell me easily which ones came from counsel and which ones you may have found on your own?

A. No, not easily.

Q. All right. Same question with respect to Exhibit B, this 28 pages of additional materials. Are you able to separate out for us easily what materials came from counsel and what materials you found on your own?

MS. O'DELL: Object to the form.

THE WITNESS: No, I can't.

BY MR. ZELLERS:

Q. The materials that are included in Deposition Exhibit 10, the articles that you list on your sheet of paper and have brought with you, there is a -- it looks like an excerpt from the IARC working group relating to asbestos and different types of asbestos; is that right?

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A. Yes.

Q. You're not an expert in asbestos; correct?

MS. O'DELL: Object to the form.

THE WITNESS: It seems like I've become pretty good at it after reading all of this material.

BY MR. ZELLERS:

Q. Well, I understand that. But you do not hold yourself out or consider yourself to be an expert in asbestos; is that right?

A. I think I've made it part of my job as an expert to become very familiar with the issues regarding asbestos and ovarian cancer.

Q. Do you consider yourself to be an expert in asbestos?

A. Can you define "expert," please.

Q. Sure. Are you an expert in the different types of asbestos: chrysotile, amosite, crocidolite, tremolite, actinolite, and anthophyllite?

A. I'm aware that there are different types of asbestos.

Q. Are you an expert in it?

MS. O'DELL: Object to the form.

THE WITNESS: I'm not sure I understand what an expert is.

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BY MR. ZELLERS:
Q. You're testifying as an expert gynecologist oncologist in this case; is that right?
A. Yes.
Q. You consider yourself to be an expert in that field; is that right?
A. Of course.
Q. Do you consider yourself to be an expert, to provide expert testimony to the jury, on asbestos and the different forms of asbestos?
A. I think I can testify to the jury what is in the literature and the impact that asbestos has on ovarian cancer risk.
Q. Prior to being retained by Dr. Thompson and Ms. O'Dell, did you have professional experience with asbestos?
A. I'm not sure what you mean by "professional experience." I don't use it in my practice.
Q. Did you research it?
A. As I said, back in 1975, when I was a resident, there was discussion about asbestos in talcum powder.
Q. Did you consider yourself to be an expert in asbestos before you were retained by Dr. Thompson and Ms. O'Dell?

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MS. O'DELL: Object to the form.
THE WITNESS: I was aware of issues with asbestos in terms of carcinogenic potential for mesothelioma and ovarian cancer.
BY MR. ZELLERS:
Q. Is that a yes, you considered yourself to be an expert in asbestos prior to being retained in this matter?
MS. O'DELL: Object to the form. I think he stated he was an expert in the health effects.
MR. ZELLERS: The doctor can answer the questions.
MS. O'DELL: He did answer the question.
THE WITNESS: That's what I was trying to say. It was the health effects, carcinogenic potential of asbestos in talcum powder and other industrial exposures.
BY MR. ZELLERS:
Q. Are you familiar with at least what the different types of claimed asbestos is in talcum powder?
A. Yes.
Q. And are you familiar with the health effects

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or alleged health effects of those different types of asbestos?
A. Yes.
Q. Did you consider yourself to be an expert in asbestos prior to being retained in this litigation in 2017?
MS. O'DELL: Objection. Asked and answered.
THE WITNESS: I don't know when I morphed into feeling I knew more about asbestos than I did in 1975.
BY MR. ZELLERS:
Q. Your -- the -- strike that.
What gives you expertise, in your view, as an expert in asbestos is the reading that you have done since being retained in this matter; is that right?
MS. O'DELL: Objection to the form. Misstates his testimony.
THE WITNESS: The knowledge that I've gained over time, including during this preparation for this deposition and my report.
BY MR. ZELLERS:
Q. When you were contacted by Dr. Thompson, did you consider yourself to be an expert in asbestos at

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that time?
MS. O'DELL: Object to the form.
THE WITNESS: Again, I've told you what I knew about asbestos at that time, and I've learned more since then.
BY MR. ZELLERS:
Q. Can you answer my question?
Did you consider yourself to be an expert in asbestos when you were first contacted by Dr. Thompson?
A. Again, I'm stuck with what -- how you define asbestos -- how you define an expert.
Q. You're an expert who -- an expert is someone who has a special expertise in a matter that peers would look to as a person and a resource.
Do people look to you as a resource on asbestos?
A. People looked to me for a long time with regard to -- as a resource with regard to asbestos and its effects on the female genital tract and ovarian cancer.
Q. So that's a yes, people have come to you for some number of years as an expert on asbestos?
A. Patients have.
MS. O'DELL: Object to the form. It

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misstates his testimony.
MR. ZELLERS: Well, I'm trying to get an answer to my question.
MS. O'DELL: I think he answered your question.
THE WITNESS: Patients have come to me as an expert in this topic as it relates to their health.
BY MR. ZELLERS:
Q. How about your peers? Do your peers come to you as an expert in asbestos at any time?
A. I have different groups of peers. My gynecologic oncology colleagues, I don't think I'm any more of an expert than they are.
On the other hand, a general obstetrician and gynecologist, an internist, a family medicine physician, a pediatrician would consider me an expert.
Q. And that -- so my question very simply is do your peers come to you as an expert in asbestos?
MS. O'DELL: Object to the form. Asked and answered.
THE WITNESS: I have lots of different levels of peers, is what I was trying to describe.
BY MR. ZELLERS:
Q. The second article that you brought and

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placed in your "Asbestos Ovarian Cancer" folder is an article by Reid. States at the top, published online first May 24, 2011, in Cancer Epidemiology, "Biomarkers & Prevention"; is that right?
A. Yes.
Q. The third article is "Occupational Exposure to Asbestos and Ovarian Cancer." This is a paper with the first author of Camargo. It appears that it was published in Environmental Health Perspectives, September 2011; is that right?
A. Yes.
Q. The last paper that you included in your folder was an article on ovarian cancer and asbestos, first named author Graham. It was received -- is this 1967?
A. Yes, sir.
Q. You brought with you, which we will mark as Exhibit 11, a folder captioned "EPI." Is that right?
A. Yes.
(Exhibit No. 11 was marked for identification.)
BY MR. ZELLERS:
Q. The first page, are these your notes to help you in terms of answering my questions relating to the epidemiology of ovarian cancer and talcum powder?
A. Yes, sir.

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Q. Did you prepare these notes?
A. Yes.
Q. First paper you list here is -- or have brought with you included in this folder and highlighted is Gates, which was published November 12th of 2009; is that right?
A. Yes.
Q. You also have brought a paper, HHS Public Access, "Douching, Talc Use," Epidemiology, 2016. First author is Gonzalez; is that right?
A. Yes, sir.
Q. Then you have another collection of materials with some additional handwritten notes, also in what we have marked as Exhibit 11, your "EPI" folder. And at the top of your handwritten notes, which appear on two Post-its, it's "Penninkilampi."
That is a study that you have written down along with some other notes, and you have brought that with you in your folder; is that right?
A. Yes.
Q. You have brought the Berge paper, dated May 18, 2018, European Journal of Cancer Prevention. You have that in your folder; correct?
A. Yes.
Q. You have the Langseth paper that was accepted

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for -- well, strike that -- that was published in Journal of Epidemiol. Community Health, 2008; is that right?
A. Yes.
Q. And then finally, you have in your folder the Taher -- T-A-H-E-R -- paper, which appears to be -- is this a 2018 or 2019 paper, if you know?
A. I don't know.
Q. Was the Taher paper something that was provided to you by counsel for the plaintiffs?
A. Yes.
Q. Was the Health Canada assessment something that was provided to you by counsel for plaintiffs?
A. Yes.
Q. You've got a folder on animals with a couple of very brief notes. We've marked your folder on animals as Exhibit 12.
(Exhibit No. 12 was marked for identification.)
BY MR. ZELLERS:
Q. First paper we have is the Keskin article from Gynecologic Obstetrics, 2009. Keskin is spelled K-E-S-K-I-N. Is that right?
A. Yes, the spelling's correct.
Q. The next paper is the Hamilton paper. It looks like it was published in 1984. The other

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authors are Fox, Buckley, Henderson, and Griffiths. It was received for publication in 1983.

Is that right?

A. Yes.

Q. Are these studies that you found, these animal studies, or are these studies that were provided to you by counsel for the plaintiffs?

MS. O'DELL: Object to the form.

THE WITNESS: I think it's some of both.

BY MR. ZELLERS:

Q. Well, there's only two that are here. So did you find and review the Keskin paper?

A. I found it and reviewed it, yes.

Q. Not provided to you by counsel; is that right?

A. Can I see them both?

Q. Sure. Of course.

(Document was handed to the witness.)

THE WITNESS: I think I printed this online, off of PubMed.

BY MR. ZELLERS:

Q. And my question is a little different.

Are these articles that you were made aware of by plaintiffs' counsel, or are these articles that

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you found in any research that you did after being retained in this matter?

A. I understand your question.

Yes, I researched and found these as I did my PubMed search.

Q. All right. Latency, Exhibit 13.

(Exhibit No. 13 was marked for identification.)

BY MR. ZELLERS:

Q. You've got a couple of handwritten notes, just a couple of articles in here. One is "The latency period of mesothelioma among a cohort of British asbestos workers (1978-2005)"; and also "Latency Period for Malignant Mesothelioma" by Dr. Lanphear, which is dated -- well, we'll have to just let the record -- it was uploaded in 2016 by the author.

Are these materials that you found in your search and have put together, or are these articles that were provided to you by counsel?

MS. O'DELL: Object to the form.

THE WITNESS: May I see that again?

BY MR. ZELLERS:

Q. Sure.

(Document was handed to the witness.)

THE WITNESS: I believe these are both

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articles that I identified in my literature search.

BY MR. ZELLERS:

Q. Did you find any articles on the latency period of ovarian cancer in women?

A. The latency at the time of exposure to asbestos or talcum powder?

Q. Yes.

A. I think it's clear that there has to be a latency period, and it's probably very parallel, in my opinion, to the latency period for mesothelioma and many other cancers that requires decades of exposure before one develops ovarian cancer.

Q. Can you be any more precise than "decades of exposure"?

MS. O'DELL: Object to the form.

THE WITNESS: No more precise than these papers that talk about the latency for mesothelioma --

BY MR. ZELLERS:

Q. You believe --

A. -- which run the gamut from 22 to 32 years in one paper and 20 to 40 years in another paper.

Q. You believe that the latency period for ovarian cancer is the same as the latency period for mesothelioma; is that right?

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MS. O'DELL: Object to the form.

THE WITNESS: I believe it should be very close.

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(Exhibit No. 14 was marked for identification.)

BY MR. ZELLERS:

Q. The last folder that you brought with you is the -- is titled or captioned "Asbestos Fibers Talc Longo, etc."

Is this also a folder that you prepared?

A. Yes, sir.

Q. You've got a number of handwritten notes and calculations here; is that right?

MS. O'DELL: Object to the form.

THE WITNESS: I'm not sure it's calculations. It's notes taken from the papers.

BY MR. ZELLERS:

Q. You cite and have brought with you a report, Longo, January 15th, 2019.

Is that the updated report that was referred to earlier?

A. That's my understanding.

Q. You've got, looks like, an exhibit from the Hopkins deposition; is that right?

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A. Yes.
Q. You have an article by Blount, "Amphibole Asbestos in Vermont Talc"; is that correct?
A. Yes.
Q. That's got an Imerys Bates number on it.
Is that where you obtained that document?
MS. O'DELL: Object to the form.
THE WITNESS: I obtained it from counsel.
BY MR. ZELLERS
Q. And then you also have the Pier deposition exhibit in your folder; is that right?
A. Yes.
Q. Have we now identified all of the materials that you have reviewed and relied upon in formulating your opinions in this matter?
A. Above and beyond these folders, the other folders that we have here are included in my reliance.
Q. Your reliance list and your reference list; is that right?
A. Yes.
Q. Exhibit A, just so we are complete here, is your CV, or curriculum vitae, as of the time that your report was published; is that right?
(Exhibit No. 15 was marked for identification.)

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BY MR. ZELLERS:
Q. And your report was published or provided and signed in November of 2018?
And that's too many questions in one.
You attached an exhibit, Exhibit A, to your report, which we have marked as Exhibit 5; is that right?
MS. O'DELL: Is it -- Exhibit 15 is the --
MR. ZELLERS: So Exhibit 15 is -- Deposition Exhibit 15 is a copy of Exhibit A to Dr. Clarke-Pearson's report, which we marked as Exhibit 5.
BY MR. ZELLERS:
Q. Number one, is that correct? Is this your CV?
A. This is my CV at the time my report was submitted.
Q. Is there a date on this curriculum vitae?
A. I don't believe so.
Q. Was it accurate and complete as of November of 2018?
A. I'm just checking to see what my most recent reference was in here. I try to keep it up to date.
Yes, I believe it was correct at the time

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that this was submitted in November 2018.
Q. Are there any updates to your curriculum vitae that you believe in any way are relevant to the opinions you're giving here today?
A. I understand. No, there's no -- nothing relevant to add.
Q. I did not tell you at the beginning, but if at any time you need to take a break and get up and stretch, just tell me and we'll do that.
A. Okay.
MR. ZELLERS: Same goes for you as well, Counsel.
MS. O'DELL: Thank you.
BY MR. ZELLERS:
Q. Did anyone assist you with your review and research and preparation of your report in this matter other than counsel?
A. No, sir.
Q. You were able to do the research that you felt you needed to do to answer the questions that were posed to you by counsel for the plaintiffs within the 20 hours that are identified in your invoice, Exhibit 2, between April 17th of 2017 and November 4th of 2018?
A. That's what I billed for. As I sort of

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indicated earlier, I'm not very diligent on marking down every minute or every hour that I spend. So that's what I billed for. It's close to what time I spent.
Q. That's your best estimate of the time that you had spent on this matter through the preparation of your report, which we marked as Exhibit 5; is that right?
A. That's correct.
Q. When were you first asked to prepare a report?
A. I'm not sure I can answer that question. It was obviously after I'd been retained and after I'd had the opportunity to review materials to be able to formulate an opinion.
Q. Other than Ms. O'Dell and Dr. Thompson, what other attorneys for the plaintiffs in the MDL talcum powder litigation have you met with or communicated with?
A. I met Ms. Brown yesterday for the first time.
Q. Anyone else?
A. No, sir.
Q. Do the -- strike that.
Does your invoice, Exhibit 2, approximate the meetings and discussions that you had with

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Dr. Thompson and Ms. O'Dell up and through the production of your report in November of 2018?

MS. O'DELL: Objection. Form.

THE WITNESS: I believe so.

BY MR. ZELLERS:

Q. Since then, what other time have you spent with the attorneys for plaintiffs relating to this matter?

A. I've had one meeting, I believe in early January, for an hour and a half or two --

Q. Was that an in-person meeting or --

A. Yes, it was in person.

Q. Was that here in Chapel Hill?

A. Yes.

Q. Was that with Ms. O'Dell and Dr. Thompson?

A. Yes.

Q. Anyone else?

A. No.

Q. Any other meetings that you've had with counsel preparing for your deposition?

A. This past Saturday and Sunday.

Q. Did you meet with the three plaintiffs' counsel who are here today?

A. Ms. O'Dell and Dr. Thompson on Saturday, and Ms. Brown joined us on Sunday.

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Q. What amount of time did you spend, total, on Saturday and Sunday with counsel preparing for the deposition?

A. I'd estimate probably four to five hours on Saturday and about five to six hours on Sunday.

Q. Anything else you did to prepare for your deposition?

A. I reviewed a lot of materials here to be really fresh on it. That's why you see these folders.

Q. Anything else you did to prepare for your deposition?

A. I'm not sure I understand what else I might do.

Q. Did you talk to anyone other than counsel for plaintiffs?

A. I see. No, I didn't.

Q. Did you speak to any of your colleagues about this?

A. No, sir.

Q. The total amount of time that you've spent, you would approximate to be the 20 hours that are reflected on Exhibit 2, plus an additional 60 hours up until today when we started your deposition?

A. That would be my approximation, yes.

Q. Have you been retained in any other talcum powder proceeding, aside from the talcum powder MDL?

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A. No.

Q. What percent of your professional time do you spend working as a consultant?

A. With regard to medicolegal expert witness work?

Q. Yes.

A. What percent? I'd say probably 5 percent in this past year, less than that in the preceding several years.

Q. What percent of your income is from consulting on litigation matters?

A. None of my income.

Q. You receive no income as an expert witness consultant on litigation?

A. No.

Q. Where does the money that you're billing for your services as an expert witness in this case go?

A. The rules that we have at University of North Carolina is that any revenue, if you will, from expert witness work is considered clinical revenue and is sent to the practice plan.

Q. Does your income, at least in part -- is it determined by the income you bring into the university?

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A. The compensation plan doesn't account for the income we bring in.

Q. Your testimony is that doesn't matter what grants you may bring in, it doesn't matter what expert witness consulting you may do or what income you may generate, it has no effect on your compensation; is that right?

MS. O'DELL: Object to the form.

THE WITNESS: The Department of Obstetrics & Gynecology at the University of North Carolina, of which I'm the chair, the compensation plan, the base salary is based on the AAMC median income based on subspecialty.

So a maternal-fetal medicine physician, based on their rank -- assistant, associate, and full professor -- has a different median income than does a gynecologic oncologist, but it's pegged to national standards.

BY MR. ZELLERS:

Q. Is there any type of bonus or additional compensation that someone in your department, including yourself, can earn?

A. Yes.

Q. How or what are the factors in terms of bonus compensation or additional compensation?

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A. Clinical relative value units that are generated by a faculty member that exceed the 60th percentile are then attributed to that faculty member. The percent of the number of faculty members' RVUs that are generated as a whole are then divided out amongst the pot of money, if you will, that's available for incentive distribution. And that amount of money depends upon the department's overall financial status.

Q. Do grants that are brought into the university by members of your department have any impact or part in this incentive distribution calculation?

A. Yes.

Q. Do -- or strike that.

Does any income from litigation consulting have a part in this incentive distribution?

A. No.

Q. Are you -- you are in charge of the department; is that right?

A. I'm the chair of the department.

Q. Do you have to balance the books in terms of money in and money out?

A. Yes, sir.

Q. Does income that you generate from litigation

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consulting help you balance the books of the department?

A. Yes.

Q. The Deposition Exhibit 3, your list of testimony that you've given in the past five years, is that now accurate and complete?

A. Yes, sir.

Q. Have all of the testimonies you've given that are listed on Exhibit 3, are those all deposition testimony? Or have you testified at trial?

A. Let me take a look at them.

The Edmonson and Lee, I testified at trial. Rappaport, I testified at trial. Pizzirusso, I testified at trial. The latter two that I -- are just depositions.

Q. Is it accurate you did not give deposition testimony in Edmonson, Rappaport, and Pizzirusso?

A. No, that's not accurate.

Q. Well, should those depositions also be included in this list of testimonies?

A. I don't know exactly what you asked for. I -- this is either depositions or testimony that I made in court.

Q. Did you give a deposition in Edmonson in the past five years?

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A. Yes.

Q. Is that included in the disclosure that was given to us today, Exhibit 3?

A. I considered it as deposition and trial testimony.

Q. So there were two testimonies, both of which you gave on December 12th of 2014; is that right?

A. No. That was probably when we submitted our invoice. I got this information from my billing department.

Q. So Edmonson really should be two testimonies; is that right?

A. Yes. Deposition --

Q. And the deposition --

A. A deposition and trial testimony.

Q. And the date you've given here relates to your invoice, not to when you provided the testimony?

A. I believe so.

Q. And the same answer with respect to Rappaport. The date on Exhibit 3 doesn't relate to when you provided the testimony; is that right?

A. That's right. And I had a deposition and trial.

Q. And, lastly, with respect to the Pizzirusso matter, the date doesn't relate to when you provided

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the testimony; correct?

A. That's correct.

Q. And it was actually a deposition and trial testimony in those matters; is that right?

A. Yes.

Q. Have you ever been retained in a case involving asbestos?

A. No.

Q. Have you ever been retained in a case involving cosmetic products?

A. No, sir.

Q. Did you review any of the expert reports of the other experts that have been retained by the plaintiffs in the MDL talcum powder litigation?

MS. O'DELL: Other than Dr. Longo, which he's testified to.

MR. ZELLERS: I'd like to hear it from the doctor, but, yes, other than Dr. Longo.

THE WITNESS: I've read a lot of things. Not many reports, so I don't recall exactly if I -- may I ask counsel, since we've been working?

BY MR. ZELLERS:

Q. Well, no, because I really want it to be your testimony. If you don't understand -- and I should have told you this up front. If you have to guess or

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speculate to answer my question, tell me you can't answer it because it would call for a guess or speculation.
A. Okay. I can't answer that.
Q. You don't recall, as you sit here, other than Dr. Longo's updated report, reviewing any other expert reports in this litigation; correct?
MS. O'DELL: Object to the form.
THE WITNESS: I reviewed Dr. Longo's original report and now the updated report.
BY MR. ZELLERS:
Q. Other than those reports, at least as you sit here, you don't have a memory of reviewing other expert reports in this matter; is that right?
A. I don't recall.
Q. Do you recall reviewing any defense expert -- or strike that.
Do you recall reviewing any other expert reports in any talcum powder litigation other than the MDL?
A. No.
Q. Have you communicated about the litigation -- the MDL talcum powder litigation -- with anyone other than plaintiffs' counsel?
A. I'm required to communicate that to the

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hospital counsel, and I have.
Q. Who is the hospital counsel?
A. Her name is Glenn -- G-L-E-N-N -- George.
Q. Does she work for the university directly or is she in private practice, if you know?
A. She works for the University of North Carolina Hospital as the head counsel.
Q. Have you communicated about talc as a cause of ovarian cancer with anyone other than the plaintiffs' counsel?
A. As it regards to this case?
Q. Yes, as it regards to this case and your opinion that talcum powder used in the perineal region by women is a cause of ovarian cancer.
A. I've communicated to the immediate past president of the Society of Gynecologic Oncology that I think that they should investigate and offer a committee opinion on the topic.
Q. Who is the -- past president you said you communicated with?
A. Past president.
Q. Who is that?
A. Her name is Laurel Rice, R-I-C-E.
Q. When did you have that communication with Dr. Rice?

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A. Sometime after I formed my opinion. I'm not sure. I'm in communication with Dr. Rice quite often. She's a friend of mine.
Q. Was it before or after you prepared your report --
A. It was after my report.
Q. So sometime after November --
A. 16th.
Q. -- 16th of 2018; is that right?
A. Yes.
Q. Any other communication you've had with anyone other than counsel for plaintiffs regarding your opinion that talc is a cause of ovarian cancer?
A. No.
Q. Have you reviewed any deposition or trial testimony from any of the talcum powder cases?
A. Yes. I'm blanking on her name. The GYN oncologist, Judy -- one of the experts on the plaintiffs' side that --
Q. Judy Wolf?
A. Yeah, Judy Wolf.
Q. Do you know Dr. Wolf?
A. I've met her once.
Q. Have you had any discussions with her about the subject matter of your opinions in this case with

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Dr. Wolf?
A. I've had no communication with Dr. Wolf whatsoever.
Q. You reviewed her deposition transcript in preparation for today; correct?
A. Yes.
Q. Any other deposition transcripts or trial transcripts in the talcum powder litigation or any talcum powder case that you have reviewed?
A. Reviewed -- I can't remember the name -- Pinkerton, maybe. It was a toxicologist that had a deposition.
Q. Do you remember the name or do you -- did you know this toxicologist?
A. I don't know the toxicologist. I think the name was Pinkerton.
Q. Any other deposition transcripts or trial transcripts that you have reviewed?
A. No, sir.
Q. Were the transcripts of Dr. Wolf and Pinkerton, the toxicologist, provided to you by counsel for the plaintiffs?
A. Yes.
Q. Did you request any information or material from counsel for the plaintiffs that was not provided

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to you?
A. No. I think everything was provided to me that I requested.
Q. In your report and in one of your file folders, you have exhibits from the deposition of John Hopkins. And let me rephrase that. You have an exhibit from a witness by the name of John Hopkins. Are you aware of that?
A. Yes.
Q. Who is Mr. Hopkins?
A. I've been -- it's my understanding -- and I may be wrong -- that he is a former employee of Johnson & Johnson.
Q. Do you know what he did for Johnson & Johnson?
A. I believe somehow he was involved with testing of talcum powder to evaluate for products such as fibrous talc and asbestos.
Q. Do you know anything else that Mr. Tom -- Mr. Hopkins did for Johnson & Johnson?
A. No.
Q. Did you review or read his deposition?
A. I did not.
Q. Do you know who Julie Pier is?
A. Vaguely.

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Q. Who is Julie Pier?
A. My understanding is that she has also done testing on Johnson & Johnson products.
Q. Do you know where she works or by whom she is employed?
A. No.
Q. Did you read her deposition transcript?
A. No.
Q. Have you reviewed any other exhibits to the deposition of John Hopkins?
A. No, sir.
Q. Have you reviewed any other exhibits to the deposition of Julie Pier?
A. No.
Q. Is it your practice outside of litigation to rely on isolated exhibits from deposition testimony?
MS. O'DELL: Object to the form.
THE WITNESS: I think sometimes if they're meaningful, yes.
BY MR. ZELLERS:
Q. Have you ever, in any of the peer-reviewed publications that are listed in Exhibit A, cited to isolated exhibits from deposition testimony of depositions that you didn't read?
MS. O'DELL: Object to the form.

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THE WITNESS: I'm sorry. You're asking me about peer-reviewed publications?
BY MR. ZELLERS:
Q. Yes, and whether or not you have ever relied upon isolated exhibits provided to you by counsel from depositions that you have never read as support for any of your peer-reviewed publications.
A. In a peer-reviewed publication, one on occasion will cite a personal communication from a colleague or an expert.
Q. Can you answer my question?
A. "In a peer-reviewed publication, one on occasion will cite a personal communication" -- okay. So your question was -- all right.
So in my peer-reviewed publications, I would say the answer is no.
Q. What is the difference between the references which are at the end of your report that we marked as Exhibit 5 and the list of additional materials which we marked as Deposition Exhibit 6 and you included as Exhibit B to your report?
A. Those are additional materials that I reviewed in formulating my opinion, but I felt that they didn't need to be included in my report.
Q. Were the references that you listed in your

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report, Exhibit 5, the key primary materials that you're relying on?
MS. O'DELL: Object to the form.
THE WITNESS: I think that's fair to say, yes.
BY MR. ZELLERS:
Q. If you go to Exhibit 6 -- could you find that in front of you. This, again, is Exhibit B to your report. Go to page 11.
And you see, starting at the bottom of page 11 carried over to page 12, there are a number of documents that begin with "Imerys" and then have a number following them.
Do you see that?
A. Yes.
Q. Did you rely on those documents in forming your opinions?
A. I reviewed them.
Q. Can you identify for us here what those documents are?
A. I would have to go to the books to review them.
Q. Do you know how those documents were compiled?
A. They were supplied by counsel.

Q. Turning to page 13, there's a series of documents that begin with "J&J" followed by numbers. Do you see that?
A. Yes.
Q. Did you rely on those documents in forming your opinions?
A. I reviewed them, and they probably served as part of my overall opinion; but I'm not referencing them per se in my report.
Q. Can you identify or tell us what those documents are?
A. These were internal documents from J&J. I don't recall specifically what each one of these numbers represent.
Q. Do you know how they were compiled?
A. They were provided to me by counsel.
Q. Plaintiffs' counsel provided you with these select company documents that you have identified in your additional materials list; is that right?
A. Yes.
MS. O'DELL: Object to the form.
BY MR. ZELLERS:
Q. Were you provided with any documents of either Imerys or J&J by counsel for plaintiffs that you did not include or list in your additional

materials-considered list?
A. No. I believe I've listed everything that we saw.
Q. Based upon -- well, strike that.
Did you review each of these documents of Imerys and J&J that are identified in your materials-reviewed list?
MS. O'DELL: Objection. Asked and answered.
THE WITNESS: Yes.
BY MR. ZELLERS:
Q. Based upon that review, did you ask plaintiffs' counsel if there were any additional documents or documents that might put in context the documents that were selected by plaintiffs' counsel for you to review?
MS. O'DELL: Object to the form.
THE WITNESS: No, I didn't ask for that.
BY MR. ZELLERS:
Q. Outside of your work in litigation, do you, with respect to your scientific publications and work, rely on small subsets of internal company documents?
MS. O'DELL: Object to the form.
THE WITNESS: I believe this is the

first time I've been shown internal documents in a litigation.
BY MR. ZELLERS:
Q. Do you have any knowledge as to what percentage of the internal documents that have been produced in this litigation were actually provided to you and appear in your materials-considered list, Exhibit 6 to this deposition?
MS. O'DELL: Object to the form.
THE WITNESS: I do not.
BY MR. ZELLERS:
Q. Is it fair to say, Dr. Clarke-Pearson, that the only company documents that you reviewed -- either Imerys or Johnson & Johnson -- are the ones that were hand-selected by plaintiffs' lawyers and provided to you?
A. Yes, that's fair to say.
Q. Do you agree, based upon your experience and the studies that you've reviewed, that most women who used talcum powder in their perineal region begin that use before age 30?
MS. O'DELL: Object to the form.
THE WITNESS: I believe that's reasonable. I'm not aware of any data that specifically says that.

BY MR. ZELLERS:
Q. Well, the Cramer 2016 paper actually goes through and lists out the age for the folks that were included in that study first used genital powder. Is that generally familiar to you?
A. I can pull the paper if we're going to need to discuss it more, but...
Q. Well, my question is -- and you can decide if you need to pull the paper. But do you agree that, based upon your review of the literature, your personal experience, that the vast majority of women who use talcum powder in their perineal region begin that use before the age of 30?
If you need to take a look at the Cramer paper, go to page 336. This is Cramer 2016, Table 1.
A. So --
Q. I think it's a simple question --
A. Probably so.
So can you restate the question? I've lost it on the screen.
Q. Sure.
Do you agree that most women who use talcum powder in their perineal region begin that use before age 30?
A. Yes.

Q. Do you agree that, on average, women who use talcum powder in their perineal region continue that use for over 20 years?
A. Yes.
Q. It's your opinion that talcum powder causes ovarian cancer; is that right?
A. Yes, sir.
Q. What are the other causes of ovarian cancer?
A. We can talk about risk factors --
Q. No, I don't want to talk about risk factors. You have identified talcum powder as a causative factor in ovarian cancer; is that right?
A. Right.
Q. That's different than being a risk factor for ovarian cancer; is that right?
MS. O'DELL: Object to the form.
THE WITNESS: I'm not sure that's true.
BY MR. ZELLERS:
Q. Well, is it your opinion that ovarian cancer is caused by talcum powder or that talcum powder is a risk factor for ovarian cancer?
A. Ovarian cancer is caused by talcum powder.
Q. What other causes of ovarian cancer are there, in your opinion?
A. Fair enough.

Age, lack of exposure to birth control pills, lack of being pregnant -- so nulliparity -- obesity, women that have had pelvic inflammatory disease, women who use a nonhormonal-producing intrauterine device, women who have gene mutations for BRCA1, 2, or Lynch syndrome.
There are probably others; but, off the top of my head, I think that's a fairly complete list.
Q. Each of the items that you have mentioned, in your opinion, those are causes of ovarian cancer; is that right?
A. Yes.
Q. What is the difference between a risk factor and a cause?
A. They're virtually the same. A risk factor describes a cause. It does not affect every woman that has that risk factor.
Q. Is that true for all of the risk factors that you just identified?
A. Yes.
Q. Is that true for talcum powder?
A. Yes.
Q. What makes a factor cross the line from being a risk factor to being a cause?
A. Well, I think that the risk factor is the

cause, but the cause doesn't -- but the risk factor doesn't cause the cancer in every instance.
Q. Talcum powder is a risk factor for ovarian cancer; is that right?
A. And it causes ovarian cancer.
Q. Every factor that you identified for us -- age, pelvic inflammatory disease, obesity -- those are all risk factors for ovarian cancer and, in your opinion, causes of ovarian cancer; is that right?
A. Yes.
Q. If a study shows a statistically significant relationship between a risk factor and a disease, is that enough for the factor to be classified as a cause?
A. In my opinion, yes.
Q. Just takes one study; is that right?
MS. O'DELL: Object to the form.
THE WITNESS: No. Now we're talking about the totality of the evidence, and nearly all of those -- all those risk factors that I described to you that are causative for ovarian cancer, including talcum powder, there's more than just one study.
BY MR. ZELLERS:
Q. Let me ask my question again because I may not have been clear.

If a study shows a statistically significant relationship between a risk factor and a disease, is that enough for the factor to be classified as a cause?
A. I see what you're saying.
So, no, one study is not sufficient, in my opinion.
Q. Other than your discussion with Dr. Rice sometime after November 16th of 2018, what have you done to alert the medical community about the relationship between talcum powder and ovarian cancer?
MS. O'DELL: Object to the form.
THE WITNESS: That's all I've done right now.
BY MR. ZELLERS:
Q. What was your methodology for concluding that talcum powder causes ovarian cancer?
A. All right. So then we get into what I describe as my methods to come to this conclusion. And I was asked by counsel to form an opinion one way or the other.
To do that, I used very similar techniques that I use in doing peer-reviewed publications, of which I have over 250 and over 50 book chapters. I need to research the literature.

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In this case, I used a PubMed search. I also used a Google search. And I reviewed a number of textbooks. In my PubMed search, many times there were references that then I would turn to and also pull up to review; and that's where many of these publications over here in these binders come from.

As I then start working my way through it, we start -- you know, in medicine, I would call it evidence-based medicine. In this particular circumstance, Bradford Hill criteria are used to come to a conclusion. And I have my Bradford Hill summary in the back of my -- at the end of my report to show you how I came to my conclusions that talcum powder causes ovarian cancer.

Q. Anything else that you did in terms of your methodology for concluding that talcum powder causes ovarian cancer?

A. I, you know, of course, in looking at publications come to try to put some weight on the publications, whether this is something that should be given more weight or less weight.

I don't have a scoring system per se, but evaluating the size of the study, the statistical analysis, the study design, the credibility of the author, the quality of the journal that the

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publication is printed in are all things that come to my -- fit into my evaluation and help me come to my conclusion.

Q. Anything else?

A. In the end, it's a matter of the totality of what I've reviewed to bring forward my opinion based on the Bradford Hill criteria.

Q. Anything else?

A. Not that I'm aware of except for my own personal experience as a gynecologic oncologist for nearly 40 years. And I've harkened back several times already to my early training and then subsequent to that.

Q. Did you follow this same methodology with regard to the other question that you addressed, whether or not there was a biologic mechanism by which talcum powder could cause ovarian cancer?

A. Yes, sir.

Q. Do you believe that the standard for proving causation in the medical literature is the same as the one that applies in litigation?

MS. O'DELL: Object to the form.

THE WITNESS: I think that we use -- whether you want to call it Bradford Hill or whether we want to call it evidence-based medicine, those are,

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I think, pretty much interchangeable terms.

I think in evidence-based medicine probably fits more into my clinical practice, and it's my understanding Bradford Hill fits more into litigation.

BY MR. ZELLERS:

Q. Try to answer my question if you can.

Do you believe that the standard for proving causation in the medical and scientific literature is the same as the one that applies in litigation?

MS. O'DELL: Object to the form. Asked and answered.

THE WITNESS: I believe so.

BY MR. ZELLERS:

Q. Is it generally known among gynecological oncologists that talcum powder causes ovarian cancer?

A. Not until recently. I think I referred to a tipping point that's happening right now that will make more gynecologic oncologists aware of the problem.

Q. At least as of now, though, the answer would be no based upon your experience; correct?

A. My experience at the moment is that many gynecologic oncologists are starting to suspect that there is an association and that talcum powder causes ovarian cancer based on the literature and then also,

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importantly, on what the news media has been reporting.

Q. What was your methodology for focusing on certain studies and excluding or not addressing other studies in your review?

MS. O'DELL: Object to the form.

THE WITNESS: Well, I think I tried to answer that before. I was trying to put a weight to those studies that are more or less strong, if you will, and -- and others that are there but really don't have any input or bearing on my decision.

BY MR. ZELLERS:

Q. You do not discuss or address the cohort studies in your report; is that right?

A. That's true.

MS. O'DELL: Object to the form.

BY MR. ZELLERS:

Q. Would you agree that, if you had only looked at the cohort studies in this case, that you would not have been able to opine that talcum powder causes ovarian cancer?

MS. O'DELL: Object to the form.

THE WITNESS: Exactly why I tried to do a full literature search and included case-control studies.

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BY MR. ZELLERS:
Q. You believe -- well, strike that.
You have published a number of articles on ovarian cancer; is that right?
A. I believe so.
Q. In any of those articles, have you published your theory that baby powder causes ovarian cancer?
MS. O'DELL: Object to the form.
THE WITNESS: The intention of those articles was not to address causation or risk factors.
BY MR. ZELLERS:
Q. Is the answer no, that you have not, at least in those publications, discussed your theory that baby powder causes ovarian cancer?
MS. O'DELL: Object to the form.
THE WITNESS: Those papers were not intended to discuss risk factors associated with talcum powder, so the answer is no.
BY MR. ZELLERS:
Q. Have you conducted any tests or experiments to confirm your theory that talc migrates from the perineum to the ovaries?
MS. O'DELL: Object to the form.
THE WITNESS: It's my opinion -- and this is not a theory -- that it's well established in

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the gynecologic community that talc can migrate along with other particles from the perineum to the ovarian surface and fallopian tube.
BY MR. ZELLERS:
Q. Try and answer my question if you can.
Have you, Dr. Clarke-Pearson, conducted any tests or experiments to confirm the theory that talc migrates from the perineum to the ovaries?
MS. O'DELL: Object to the form.
THE WITNESS: No, I have not.
BY MR. ZELLERS:
Q. Have you, Dr. Clarke-Pearson, conducted any tests or experiments to confirm your theory that talc causes cancer via inflammation?
MS. O'DELL: Object to the form.
THE WITNESS: It's not my theory; it's my opinion that talc causes ovarian cancer through inflammation.
I have not done any studies to confirm my opinion.
BY MR. ZELLERS:
Q. Can you identify a single article that identifies inflammation anywhere in a woman's reproductive tract resulting from external genital talc application?

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MS. O'DELL: Mike, after Dr. Clarke-Pearson answers this question, we've been going about an hour and 50 minutes. If we could take a break, that would be great.
MR. ZELLERS: That's fine. I've got one more after this, and then would be glad to take a break.
BY MR. ZELLERS:
Q. Dr. Clarke-Pearson, can you answer that?
A. I thought I had a folder on inflammation here. I don't think you put it under your pile. But, at any rate, I think I have seen evidence that talc can cause inflammation in the ovary.
Q. Let me ask my question again.
Can you identify a single article that identifies inflammation anywhere in a woman's reproductive tract resulting from external genital talc application?
MS. O'DELL: Object to the form.
THE WITNESS: I don't believe so, that I can quote for you right now.
BY MR. ZELLERS:
Q. Can you cite a single study, animal or human, that traces externally applied talc up through the reproductive tract to the ovaries?

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A. I think that's well accepted, as I said, in the gynecologic community, that the vagina is open to the outside world, if you will, there's no lid at the opening of the vagina, and that particles of talc can migrate from the vulva and perineum up through the uterus and onto the ovaries.
Q. Now I need you to answer my question. Do you need me to repeat it?
MS. O'DELL: Well, Counsel, won't you be courteous of the witness. He answered your question. You may not have liked the answer. And you happy to ask another question.
MR. ZELLERS: No, he did not answer my question.
MS. O'DELL: He did answer your question.
MR. ZELLERS: The record will reflect he did not. And I think both of us, all of us, are being cordial and professional.
If, at any time, Dr. Clarke-Pearson, you don't think I'm being professional, let me know. Okay?
THE WITNESS: Sure.
BY MR. ZELLERS:
Q. My specific question to you is can you cite

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any study, animal or human, that traces externally applied talc up through the reproductive tact to the ovaries?

MS. O'DELL: Object to the form.

THE WITNESS: So by study, you mean a peer-reviewed publication?

BY MR. ZELLERS:

Q. Yes.

A. I cannot.

MR. ZELLERS: Let's take a break.

THE VIDEOGRAPHER: Going off the record at 10:50 a.m.

(Recess taken from 10:50 a.m. to 11:04 a.m.)

THE VIDEOGRAPHER: Back on record at 11:04 a.m.

BY MR. ZELLERS:

Q. Dr. Clarke-Pearson, do you treat women who have ovarian cancer and other gynecological disease?

A. I've treated hundreds of women with ovarian cancer, put them through radical surgical procedures, including bowel resections and removing their spleen to get their cancer out. I've given them chemotherapy. We've had some successes. I've taken care of a lot of patients throughout the remainder of their life as they died from ovarian cancer.

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So to answer your question, yes.

Q. Do you also counsel women who are at high risk for ovarian cancer?

MS. O'DELL: Object to the form.

THE WITNESS: Yes.

BY MR. ZELLERS:

Q. Ovarian cancer is a complex disease; correct?

A. Cancer, in general, is a complex disease. I wish we knew more about it.

Q. No one knows for sure how ovarian cancer develops; is that right?

MS. O'DELL: Object to the form.

THE WITNESS: I think we have some strong opinions based on scientific research, and we continue to research further in terms of the genetics and mutations that go along with developing ovarian cancer.

BY MR. ZELLERS:

Q. Is it true that no one knows for sure how ovarian cancer develops?

MS. O'DELL: Object to the form.

THE WITNESS: I guess no one knows for sure.

BY MR. ZELLERS:

Q. You refer in your report to there being

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several theories as to the origin of ovarian cancer; is that right?

MS. O'DELL: Object to the form.

THE WITNESS: Yes.

BY MR. ZELLERS:

Q. Do you agree that, although some risk factors, like age or BRCA genetic mutations have been identified, it's impossible to say for sure what the cause of ovarian cancer was for any individual woman?

MS. O'DELL: Object to the form.

THE WITNESS: Well, we know that the cause is a genetic mutation that allows the ovarian cancer -- that ovarian cell that was normal to become a malignant cell and loses its regulation and growth.

BY MR. ZELLERS:

Q. Do you agree, though, that it is impossible to say for sure what the cause of ovarian cancer was for any individual woman?

MS. O'DELL: Object to the form.

THE WITNESS: The cause is always a gene mutation.

BY MR. ZELLERS:

Q. Is it your testimony that you are able to identify the cause of ovarian cancer in all cases?

MS. O'DELL: Object to the form.

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THE WITNESS: I can't identify the gene mutation in all cases, no.

BY MR. ZELLERS:

Q. Is it impossible to say for sure what gene mutation or other cause of ovarian cancer was for any individual woman?

MS. O'DELL: Object to the form.

THE WITNESS: In some individual women, we can identify the cause, for example, the mutation of the BRCA1 and 2 gene. We can also do genetic profiling more and more these days, identifying a number of gene mutations that then lead to the malignancy.

BY MR. ZELLERS:

Q. Other than BRCA1 and 2, do you agree that it is impossible to say for sure what the cause of ovarian cancer was for any individual woman?

MS. O'DELL: Object to the form.

THE WITNESS: There are more gene mutations than BRCA 1 and 2. There's PD1 and others that I don't have off the top of my head that are now being identified.

BY MR. ZELLERS:

Q. Other than when a specific gene mutation can be identified, is it impossible to say for sure what

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the cause of ovarian cancer was for any individual woman?
MS. O'DELL: Object to the form.
THE WITNESS: In -- to answer your question, what I think I understand your question being, if we can't identify a gene mutation, then we don't know what caused it. Is that what you're asking me?
BY MR. ZELLERS:
Q. Yes.
A. Then the answer would be, yes, we don't know.
Q. In your practice, do you diagnose what caused your patients' ovarian cancer?
A. We do genetic profiling, as is a relatively new approach to trying to approach causes, and also personalized treatment for patients with ovarian cancer.
Q. Other than genetic profiling, in your practice do you diagnose what caused your patients' ovarian cancer?
MS. O'DELL: Object to the form.
THE WITNESS: We don't. There's no -- I don't think anybody can.
BY MR. ZELLERS:
Q. In your practice, do you tell your patients

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what caused their ovarian cancer other than with respect to genetic profiling?
MS. O'DELL: Object to the form.
THE WITNESS: No.
BY MR. ZELLERS:
Q. Have you ever given any presentation on the relationship between talcum powder and ovarian cancer?
A. No.
Q. Have you ever spoken at a conference or meeting of the American College of Obstetricians and Gynecologists, or ACOG, about the relationship between talcum powder and ovarian cancer?
A. Not that I recall.
Q. Have you ever spoken at a conference or meeting of the Society of Gynecologic Oncology, or SGO, about the relationship between talcum powder and ovarian cancer?
A. No.
Q. Does your institution, the University of North Carolina, advise women that perineal use of talcum powder causes ovarian cancer?
A. Well, again, back to my point of the tipping point in this whole discussion. And so at this juncture, we are considering adding that to our patient intake form, to ask for that information, and

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then also advise.
Q. As of today, it's not part of the patient intake form; is that right?
A. As of today, no.
Q. As of today, the University of North Carolina and the department that you chair do not advise women that perineal use of talcum powder causes ovarian cancer; correct?
MS. O'DELL: Object to the form.
THE WITNESS: That's correct.
BY MR. ZELLERS:
Q. Do you teach residents about talc as a potential risk factor?
A. It is listed as a potential risk factor today, and I think in the very near future it will be considered a risk factor and a causative factor.
Q. When did you first start doing that, teaching residents about talc as a potential risk factor?
A. Well, I think it's been in the literature for a good while as a potential risk factor.
Q. My question is when did you first begin teaching residents about talc as a potential risk factor?
A. I think from the time that I was starting to teach residents in 1975 -- well, I was a resident in

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'75 -- 1979 when I finished my residency and started teaching residents.
Q. Do you today ask any of your own patients if they used talcum powder as a routine screening question?
A. I think that would be very inappropriate for a woman who has advanced ovarian cancer to try to find and cause her to feel guilt that she did something to cause ovarian cancer. My situation is one of trying to take care of women that have ovarian cancer.
Q. Have you ever told a patient that talcum powder caused her ovarian cancer?
A. No.
Q. Have you ever recommended increased screening or monitoring for ovarian cancer based on a patient's prior use of talcum powder products?
A. Not yet.
Q. Have you ever recommended that a patient who had a history of using talcum powder undergo prophylactic surgery to remove the fallopian tubes or ovaries because of her talcum powder use?
A. I think that is likely to become a discussion in the near future, and we would have to balance the risks of surgery versus the risks of developing ovarian cancer.

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Q. As of today, you have not; is that right?
A. That's correct.
Q. Have you ever asked your patients about their exposure to asbestos in the course of taking their medical histories?
A. No.
Q. Are you familiar with screenings for asbestos exposure?
A. I'm not familiar with that.
Q. Do you ask your patients about their occupational history?
A. I often -- yes, most of the time I find out what the patient does outside the home.
Q. Do you ask your patients about the occupational history of their parents?
A. I do not.
Q. Do you ask your patients about their spouse's occupational history?
A. Sometimes.
Q. Do you ask what kind of buildings your patients have either lived in or do live in?
A. No.
Q. Do you ask about the kind of buildings that your patients either work in or have worked in?
A. Have not.

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Q. In 1993 you coauthored an article on the mutations of the p53 gene and ovarian cancer; is that right?
A. I believe so. I was a coauthor.
Q. That study concluded that p53 mutations in ovarian cancer arise because of spontaneous errors in DNA synthesis and repair rather than direct interaction with -- strike that -- rather than the direct interaction of carcinogens with DNA; is that right?
MS. O'DELL: He needed --
THE WITNESS: I would have to see that paper. 1993 was a long time ago. It was kind of our lab. And I was not in the lab, but I was a coauthor.
MR. ZELLERS: Deposition Exhibit 16 is the paper on which you were an author. First named author was Kohler.
(Exhibit No. 16 was marked for identification.)
BY MR. ZELLERS:
Q. Take just a quick look at that, and I have a specific question for you.
This is your paper that you were a coauthor on back in 1993; is that right?
A. Allow me to read this a little bit more.
Q. Sure.

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A. All right. I think I can answer this. This is a long time ago.
Q. As -- and let me just repeat my question, and I'm specifically looking at the statement toward the bottom of the third column on page 1 of the publication.
The study concluded that p53 mutations in ovarian cancer arise because of spontaneous errors in DNA synthesis and repair rather than the direct interaction of carcinogens with DNA; is that right?
A. That's what it reads.
Q. That would be inconsistent with the idea that exposure to talcum powder causes errors in DNA synthesis and repair that lead to cancer; is that right?
MS. O'DELL: Object to the form.
THE WITNESS: No, that's not -- that's not correct.
BY MR. ZELLERS:
Q. Why is that not correct?
A. So the inflammatory response of the ovarian epithelium to talcum powder then leads to gene mutations, and there is mounting evidence that that's happening in work that's being written and presented by Dr. Saed in particular.

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Q. Does your paper -- the 1993 paper -- discuss inflammation?
A. No. That wasn't part of the question that was being pursued in this laboratory investigation.
Q. Your paper in 1983 [sic] states that (as read):
"Consistent with data from epidemiologic studies that failed to demonstrate a convincing relationship between ovarian cancer and exposure to environmental carcinogens."
Is that right?
MS. O'DELL: Object to the form.
BY MR. ZELLERS:
Q. And I'm looking again at the first page of your article at the bottom -- or right above the line in the third column.
A. You've read that correctly. I would have to reread this paper -- it's more than 20 years old -- because I'm not continue -- I'm not currently aware of the investigation that we did looking at carcinogens.
Q. In 2009, you published an article entitled "Screening for Ovarian Cancer." Is that right?
A. I'd have to see the article.

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MR. ZELLERS: We'll mark your 2009 article as Deposition Exhibit 17.
(Exhibit No. 17 was marked for identification.)
THE WITNESS: Yes. Okay.
BY MR. ZELLERS:
Q. This is an article that you authored; is that right?
A. Yes, it was printed in The New England Journal. I was invited to write this clinical review.
Q. This is an article that is captioned "Screening for Ovarian Cancer." Is that right?
A. Yes.
Q. This is many years before you were retained by Dr. Thompson and plaintiffs' counsel in the talcum powder litigation; is that right?
A. Yes.
Q. In this article, you discussed risk factors for ovarian cancer. And I'm looking at the second paragraph on page 1.
A. The first page of -- page 170?
Q. Yes. And my question, specifically, is you only discussed in this article the risk factors of family history of ovarian or breast cancer and the BRCA genetic mutations; is that right?
MS. O'DELL: Object to the form.

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THE WITNESS: That's what appears to be, yes.
BY MR. ZELLERS:
Q. You did not mention talcum powder in this article; is that right?
A. It appears I didn't mention several other risk factors. That wasn't the intent of this article.
Q. Well, in July of 2014, you appeared on a FOX News station to discuss ovarian cancer; do you remember that?
A. Vaguely.
Q. That was before you were retained by Dr. Thompson and by plaintiffs' counsel in this case; correct?
MS. O'DELL: Object to the form.
THE WITNESS: Yes.
BY MR. ZELLERS:
Q. As part of that discussion, you were asked and talked about risk factors for ovarian cancer.
Do you recall that?
A. No.
Q. Do you recall that, in that interview in 2014, July, you only mentioned age, family history of breast or ovarian cancer, and BRCA genetic mutations as risk factors?

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A. I don't recall that, but it may be on the videotape that you probably have.
Q. You did not tell the viewers that talcum powder was associated with or a cause of ovarian cancer; is that right?
A. That's correct, because at that point in time I didn't believe it was causative.
Q. It wasn't until after being retained in this case, and around the time that you concluded your review in November of 2018, that you formed that opinion; correct?
MS. O'DELL: Object to the form.
Excuse me. Go ahead.
THE WITNESS: As I was preparing to offer an opinion, I did this review and came to that opinion, yes.
BY MR. ZELLERS:
Q. If we try to put a time on it, it would be toward the latter part of 2018, once you had completed your review that you've told us about in connection with this litigation; correct?
A. Yes.
MS. O'DELL: Object to the form.
BY MR. ZELLERS:
Q. Where do practicing gynecological oncologists

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look for guidance on what the risk factors are for ovarian cancer?
A. I think a variety of sources, from -- published in many textbooks, review articles.
Q. Well, just as you don't have the time to go and research each and every potential risk factor for ovarian cancer in depth, you rely on certain organizations to do that research for you; right?
MS. O'DELL: Object to the form.
THE WITNESS: And other researchers, yes.
BY MR. ZELLERS:
Q. One organization would be the American College of Obstetricians and Gynecologists, or ACOG; is that right?
A. Yes.
Q. Another organization would be the Society of Gynecologic Oncology, or SGO; is that right?
A. Yes.
Q. Another would be the National Cancer Institute's physician data queries?
A. I probably wouldn't turn to that, but it's information available to the public.
Q. That's generally thought to be reliable information; correct?

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MS. O'DELL: Object to the form.
THE WITNESS: I'm not quite certain. I'm not familiar with that. Is this a PDQ you're talking about?
BY MR. ZELLERS:
Q. A PDQ. But you're familiar, certainly, with the National Cancer Institute; right?
A. Yes.
Q. The National Cancer Institute has funded at least some of the studies that you have been involved in; is that right?
A. As basic research and research into ovarian cancer treatment, not necessarily risk factors.
Q. Is it a reputable organization, the National Cancer Institute?
A. It's an agency that sponsors cancer research, by and large.
Q. Is that a "yes"?
A. There -- they're reputable in terms of sponsoring cancer research.
Q. You're a member of ACOG; is that right?
A. Yes, sir.
Q. You're a member of SGO; is that right?
A. Yes.
Q. You were the president of SGO from 2009 to

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2010; is that right?
A. Yeah.
Q. You've served on a number of committees for both ACOG and SGO; is that right?
A. Yes.
Q. Do you agree, generally, that the doctors and scientists in organizations like ACOG and SGO are working very hard to protect women's health?
A. Yes.
MS. O'DELL: Object to the form.
BY MR. ZELLERS:
Q. And, in forming your opinions in this case, did you consider the risk factors that ACOG and SGO recognized for ovarian cancer?
A. I was familiar with the existing risk factors that had been identified.
Q. Are you aware that, even as of today, in their patient-facing websites as well as in their publicly available information about ovarian cancer, neither ACOG nor SGO identify perineal use of talcum powder as a risk factor for ovarian cancer?
A. Again, I'm getting back to my point that we're at a point in time where it's a tipping point. And so, yes, right now, that's not posted. And I would imagine that my opinion that ovarian cancer is

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caused by talcum powder will be reflected in those statements in the future.
Q. You don't have any reason to believe that the physicians at ACOG and SGO have not kept up to date with the talc and ovarian cancer epidemiology, do you?
MS. O'DELL: Object to the form.
THE WITNESS: I think that they haven't looked at this question as in depth as I have.
BY MR. ZELLERS:
Q. How do you know that?
A. I'm quite certain of that.
Q. Well --
A. This is a huge amount of work, to spend 80 hours reviewing materials to come to my opinion. I'm not aware of any other physician that's been tasked with that job, if you will.
Q. Are there not committees on both ACOG and SGO that look into risk factors and potential causes for ovarian cancer?
A. I have served as the committee chair for the GYN Management Committee at ACOG, which publishes committee opinions. And I've also served on the practice committee, which puts out technical bulletins, now called practice bulletins.
In both cases, ACOG is asked by a member to

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consider investigating and writing an opinion about that. So if the opinion was requested by an ACOG member, that committee would then decide whether they wanted to pursue that or not.
Q. Does ACOG and SGO have committees who generally look at the risk factors for ovarian cancer?
A. Only if that committee is asked to look at that question.
Q. Any member of ACOG or any member of SGO can ask either ACOG or SGO and their respective committees to look at and evaluate a particular risk factor; correct?
A. Yes. Sure.
Q. And it's your testimony that that's never ever been done up until today?
MS. O'DELL: Object to the form.
THE WITNESS: No, it's not my testimony. I don't know what's been requested of ACOG in the past or currently.
BY MR. ZELLERS:
Q. Would it be important to you to know that Centers for Disease Control and Prevention, the CDC, does not list talcum powder or talc as a risk factor for ovarian cancer?
A. That doesn't surprise me.

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Q. The same for the Mayo Clinic. The Mayo Clinic does not list talc as a risk factor for ovarian cancer; correct?
A. I'll take your word for it.
Q. Have you received funding from the National Institutes of Health?
A. I've received funding from the National Cancer Institute, and I have received funding for physician training through the National Institutes of Health for a women's reproductive health research grant.
Q. Are you aware that NIH does not list talc as a risk factor for ovarian cancer?
A. I would have to look at their publications. That wouldn't surprise me, along with all the other agencies and foundations and organizations that you've listed previously.
Q. With respect to the National Cancer Institute, they do publish guidance for physicians on risk factors for cancer; is that right?
A. I believe so.
Q. Take a look at Deposition Exhibit 18.
(Exhibit No. 18 was marked for identification.)
BY MR. ZELLERS:
Q. Are you familiar with this publication of the

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National Cancer Institute?
A. No.
Q. This is not something that you reviewed in all of your preparation and research for rendering your opinions in this case?
A. I may have seen it, but I'm not familiar with all the details of it.
Q. Well, did you review and rely on this statement by the National Cancer Institute with regard to ovarian, fallopian tube, and primary peritoneal cancer prevention in your review of this matter?
MS. O'DELL: Object to the form.
THE WITNESS: It did not contribute to my formation of my opinion, if that's what you're asking.
BY MR. ZELLERS:
Q. Well, take a look, if you will, on page 12, 12 of 18, at the section "Perineal Talc Exposure."
Do you see that?
A. Yes.
Q. The National Cancer Institute states (as read):
"The weight of evidence does not support an association between perineal talc exposure and an

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increased risk of ovarian cancer."
Is that right?
A. That's what they say.
Q. If you go to 18 of 18, this statement was updated as of January 4th of 2019; is that right?
MS. O'DELL: Object to the form.
THE WITNESS: Yes, I see they updated that.
And I think that I do recall having seen this. And my recollection is that their references are not fully up to date too. And also, it befuddles me that the National Cancer Institute -- is that right? -- National Cancer Institute, going back to page 12, would take statistically significant clinical studies and dismiss that clinical significance -- a relative risk of 1.44, a relative risk of 1.26 -- I'm sorry -- 1.71, a relative risk of 1.2 -- and say that they're not important.
BY MR. ZELLERS:
Q. You have no personal knowledge of the analysis done by the National Cancer Institute that underlie this statement; correct?
A. I don't, and I have a hard time understanding how they came to the conclusions they have.
Q. Well, let's look at the FDA. The FDA has

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also looked at this issue, has looked at the Bradford Hill factors, and has concluded that causation has not been established as between talcum powder use -- peritoneal -- perineal talcum powder use and ovarian cancer; is that right?
MS. O'DELL: Object to the form.
THE WITNESS: I'd have to see the publication.
BY MR. ZELLERS:
Q. Well, let's take a look.
I'm handing you what we have marked as Deposition Exhibit 19.
(Exhibit No. 19 was marked for identification.)
BY MR. ZELLERS:
Q. This is a letter from the FDA. It has a date stamp at the top, April 1, 2014. It's addressed to Dr. Epstein at the University of Illinois in Chicago.
A. I think I have seen this one.
Q. FDA is another governmental entity; is that right?
A. Yes.
Q. As far as you know, the FDA is not biased one way or the other with respect to the food and drug issues that they research and opine on; is that right?
MS. O'DELL: Object to the form.

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THE WITNESS: No, that's incorrect. In my personal experience, the FDA has done a bad job in evaluating the risk of morcellation of uterine fibroids. The data that they based their black box opinion on in November of 2014 was based on inadequate review of the medical literature. And it was biased and I think clearly influenced by some outside sources.

BY MR. ZELLERS:

Q. Do you have criticisms of the FDA's review and investigation of talcum powder products?

A. I would like to reread this, because I did have some criticism in reading this.

Q. Well, my question is more general. But you would agree --

A. Yes, I have criticism. I think that they're not sufficiently evaluating all the data and evidence that's here.

Q. Does the FDA have qualified scientists and medical professionals that look at various issues, including talcum powder?

MS. O'DELL: Object to the form.

THE WITNESS: They probably have qualified people that sometimes make mistakes or sometimes have biases of their own.

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BY MR. ZELLERS:

Q. But do you agree that, on scientific issues, including the one that we're here to talk about today, whether or not talcum powder -- genital use of talcum powder is a risk factor for ovarian cancer, that's a topic on which well-qualified scientists and physicians may have differing views?

MS. O'DELL: Object to the form.

THE WITNESS: They may have differing views, yes.

BY MR. ZELLERS:

Q. Let's look at this publication from the FDA. Turn to page 4, if you will. And we are looking at Deposition Exhibit 21. Are you at page 4?

MS. O'DELL: Are we at 21 or 19?

MR. ZELLERS: Oh, I'm sorry. I misspoke. Thank you, Ms. O'Dell. Yes. So let me ask that question again.

BY MR. ZELLERS:

Q. Turn, if you will, Doctor, to page 4 of Deposition Exhibit 19.

THE WITNESS: Ms. O'Dell, may I have -- I have some notes on this letter.

MS. O'DELL: Is it in your --

THE WITNESS: No, I don't think it's in the pile.

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BY MR. ZELLERS:

Q. You have notes that are other than what you brought here today?

MS. O'DELL: I think it's in -- may be in your stack, Doctor. I'm not sure. I don't have it --

THE WITNESS: Well, I'll go through it. My recall of this is this letter is all over the place in terms of pros and cons and pros and cons. So we can work my way through it, but -- go ahead. I'm on page 4.

BY MR. ZELLERS:

Q. All right. The FDA goes through and reviews epidemiology and etiology findings; is that right?

A. That's where they start, yes.

Q. The FDA noted, in reviewing this issue, genital use of talcum powder and ovarian cancer, that "selection bias and/or uncontrolled confounding result in spurious positive associations" --

A. I'm sorry. Can you just take me to where you are on page 4?

Q. Sure. Let's look -- if we're on page 4, right above the findings or conclusion, it says (as read):

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"After consideration of the" --

A. My page 4 doesn't have findings and conclusions. "Epidemiology and etiology findings"?

Q. Yes. So we're on the same page --

A. Above this (indicating)?

Q. Underneath "epidemiology and etiology findings" --

A. Okay.

Q. -- if we go to the second paragraph, it states (as read):

"After consideration of the scientific literature submitted in support of both citizen petitions, FDA found..."

Are you with me?

A. Yes, I am.

Q. All right. No. 2 (as read):

"The FDA noted that no single study has considered all the factors that potentially contribute to ovarian cancer, including selection bias and/or uncontrolled confounding that result in spurious positive associations between talc use and

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ovarian cancer."
Did I read that correctly?
A. Yes.
Q. You would agree that there are limitations on case-control studies; is that right?
A. Yes, there are.
Q. There are difficulties in interpreting a retrospective case-control study; is that right?
MS. O'DELL: Object to the form.
THE WITNESS: I'm not sure what you mean by "difficulties."
BY MR. ZELLERS:
Q. Well, are there limitations in interpreting a retrospective case-control study?
A. There can be.
Q. What are those limitations that you're aware of based upon your experience?
A. Well, it depends upon how the study is designed, in terms of the size of the study, the -- how the -- you know, recall issue is always an issue when you're dealing with patients retrospectively. There are similar problems in cohort studies as well.
Q. My question is very simple. What are you aware of in terms of

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limitations of retrospective case-control studies?
MS. O'DELL: Object to the form. Asked and answered.
BY MR. ZELLERS:
Q. That generally apply to case-control studies.
MS. O'DELL: Object to the form. Asked and answered.
THE WITNESS: Well, there are limitations in probably -- there's a variety of limitations, depending upon the particular studies. So I think we would have to get down to a particular study. And I don't hang my weight -- or hang my hat or put the weight of my opinion on a single study.
BY MR. ZELLERS:
Q. Well, you would agree that selection bias is a potential concern in case-control studies; correct?
A. It can be.
Q. And uncontrolled confounding is a potential concern in case-control studies; is that right?
A. Yes. But if your controls are well selected, then that negates much of the bias.
Q. And, at least in this document, the FDA states that "those result in spurious positive associations between talc use and ovarian cancer risk"; is that right?

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A. That's with regard -- in the first part of their sentence to "no single study."
Q. Let's look at Conclusion 3.
"The FDA concludes that results of case-control studies do not demonstrate a consistent positive association across studies."
Is that right?
MS. O'DELL: Objection.
THE WITNESS: That's wrong. You read it right; it's wrong.
BY MR. ZELLERS:
Q. You disagree with the FDA's conclusion; is that right?
A. Yes.
Q. And I'm going to ask you all about that today --
A. Okay.
Q. -- so you'll have to chance to tell me why you disagree.
Did the FDA also state that, at least based upon its review of the epidemiology and etiology findings, that a dose response -- strike that -- that dose response evidence is lacking?
MS. O'DELL: Object to the form.

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THE WITNESS: And can you show me where you're reading that?
BY MR. ZELLERS:
Q. Sure. Conclusion 3, last part of the statement.
A. There is dose response evidence. It's not in every single study, but we are aware of dose response --
Q. Doctor, my question was, was it the FDA's conclusion, based upon the epidemiology that it reviewed as of 2014, that dose response evidence is lacking?
A. That's the FDA's opinion; that's not my opinion.
Q. Finally, the FDA found that "a cogent biological mechanism was lacking." And I'm looking at number 4, "A cogent biological mechanism by which talc might lead to ovarian cancer is lacking."
Is that the statement of the FDA, at least as of 2014?
A. The statement goes on in the same sentence to say (as read):
"Exposure to talc does not account for all cases of ovarian cancer."
Nothing accounts for all cases of ovarian

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cancer. I can't believe the FDA would even say something like this.
Q. Are you able to answer my question without editorializing?
A. I answered your question. I have to finish the whole sentence that you want me to read.
Q. Did the FDA state, as of 2014, that "a cogent biological mechanism by which talc might lead to ovarian cancer is lacking"?
MS. O'DELL: Object to the form. Asked and answered.
THE WITNESS: That's what half of the sentence says. That's what the FDA wrote.
BY MR. ZELLERS:
Q. All right. IARC, you're certainly familiar with IARC. You brought your whole monograph here with you today; is that right?
A. Yes.
MS. O'DELL: Object to the form. It's not his monograph; it's not the whole monograph -- it's multiple monographs, as you know. So don't -- don't be --
MR. ZELLERS: I haven't gone through it page by page, but it looks like it's about a 2-inch-thick monograph that he brought with him today.

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BY MR. ZELLERS:
Q. My question is, are you familiar with IARC?
A. I am.
Q. All right. IARC has addressed Bradford Hill considerations with respect to talc used in a perineal manner with respect to women -- is that right? -- in ovarian cancer?
MS. O'DELL: Object to the form.
THE WITNESS: You're asking me a question, not what the FDA is writing here now but what IARC has said?
BY MR. ZELLERS:
Q. I'm now on to IARC. So let me ask my question.
Based upon your review of the IARC monographs, it has addressed the Bradford Hill considerations; is that right?
MS. O'DELL: Object to the form.
Are you referring to all the monographs? Are you referring to a certain topic that's -- because, as you know, there are multiple monographs and they relate to different substances. So, for your specific question, that might be helpful.
BY MR. ZELLERS:
Q. Are you aware, Dr. Clarke-Pearson, that IARC

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rejected classification of talc as carcinogenic and instead assigned it to the classification of possibly carcinogenic to humans?
MS. O'DELL: Object to the form.
THE WITNESS: I think that was an IARC publication in the mid 2000s. And I'm aware of it, yes.
BY MR. ZELLERS:
Q. Are you generally familiar with the IARC categories?
A. Generally, but I'm happy to walk through them with you.
Q. Sure. Doctor, I show you Exhibit 20.
(Exhibit No. 20 was marked for identification.)
BY MR. ZELLERS:
Q. This is a one-page listing of the agents classified by the IARC monographs, Volumes 1 to 123, and it lists out the different categories that IARC classifies agents within.
You're generally familiar with --
A. Yes.
Q. -- with these classifications; is that right?
A. Yes, sir.
Q. Looking at Exhibit 20, there are 120 agents in Group 1, "carcinogenic to humans"; is that right?

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A. Yes.
Q. That's the only category in which IARC finds sufficient evidence in humans; is that right?
A. That's my understanding.
Q. And there's 82 agents in Group 2A, "probably carcinogenic to humans"; is that right?
A. I see that.
Q. It appears that IARC isn't shy about declaring something to be either a known or a probable carcinogen; is that right?
MS. O'DELL: Object to the form.
THE WITNESS: I don't know about being shy. They have their listing from their --
BY MR. ZELLERS:
Q. Well, they have over 200 agents in those two categories; is that right?
A. Yes.
Q. There's only one agent in Group 4, "probably not carcinogenic to humans"; is that right?
MS. O'DELL: Object to the form.
THE WITNESS: That's what it says.
BY MR. ZELLERS:
Q. So out of the over a thousand agents that IARC has reviewed, IARC has placed only one agent in Group 4, "probably not carcinogenic"?

A. Yes.
Q. IARC doesn't have a Group 5, "not carcinogenic," do they?
A. Not on this sheet.
Q. With genital talc, IARC has classified genital talc as a Group 2B category agent; is that right?
MS. O'DELL: Object to the form.
THE WITNESS: I'm not sure. It's just genital talc. Isn't the talcum powder of all forms?
BY MR. ZELLERS:
Q. Talcum powder is a Group 2B agent, "possibly carcinogenic to humans"; is that right?
A. Yes.
Q. That designation is based, according to the IARC definitions, on limited evidence in humans; is that right?
MS. O'DELL: Object to the form.
THE WITNESS: I would have to read what is written.
BY MR. ZELLERS:
Q. Is it your understanding that, in classifying talcum powder as a Group 2B agent, that IARC cannot rule out chance, bias, or confounding with reasonable confidence; correct?

A. I suppose you're reading that from some IARC statement that I don't have, but...
Q. That's generally your understanding; correct?
A. That would be generally my understanding, yes.
Q. Are you aware of some of the other agents that have been designated as 2B agents by IARC as possibly carcinogenic?
A. I am not.
Q. Ginkgo biloba? Are you familiar with that?
A. No.
Q. Occupational carpentry and joinery?
MS. O'DELL: I'm sorry. I missed that last one. What did you say?
BY MR. ZELLERS:
Q. Occupational carpentry and joinery.
A. I was not aware of that.
Q. Pickled vegetables?
A. I've heard that.
Q. All right. What association does the literature report between talc use and ovarian cancer?
A. Well, now we move into looking at epidemiology, in my opinion.
Q. Well, these are just a few general questions. If you need to look at your folders, please do. But

I just have a few general questions.
A. All right. Well, please go ahead.
Q. Well, are you able to tell me, generally, what association the literature reports between talc use and ovarian cancer?
A. The literature consistently shows an increased risk of developing ovarian cancer in women that are exposed to talcum powder.
Q. Generally, it's around a 1.3 odds ratio in the case-control studies; is that fair?
MS. O'DELL: Object to the form.
THE WITNESS: I would acknowledge that, yes.
BY MR. ZELLERS:
Q. All right. Do you also acknowledge that the epidemiologists consider a 1.3 odds ratio in case-control studies to be a weak or modest association?
MS. O'DELL: Object to the form.
THE WITNESS: I'm not sure what they mean by "weak" or "modest."
BY MR. ZELLERS:
Q. Would you categorize it as a weak or modest association?
A. No. I would call it a statistically

significant observation that impacts the lives of thousands of women that I've taken care of over the years and that, if talcum powder were not on the market and being used in perineal hygiene, for lack of a better word, many other women would not have died of ovarian cancer that I've taken care of.
MR. ZELLERS: Move to strike as nonresponsive.
BY MR. ZELLERS:
Q. You are unaware as to whether or not an epidemiologist would consider a 1.3 odds ratio in a case-control study to be a weak or modest association; is that right?
A. I don't understand the definition of "weak" or "modest."
Q. You're not an epidemiologist; is that right?
A. That's correct.
Q. Can you point to any peer-reviewed literature on talc and ovarian cancer that states that 1.3 odds ratio is a strong association?
A. I think --
MS. O'DELL: Object to the form.
THE WITNESS: -- it's a statistically significant association that's been consistently reported in case-control studies and in meta-analyses.

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BY MR. ZELLERS:
Q. I take it that's no to my question. Is that right? And I'll ask it again if you'd like me to.
MS. O'DELL: Object to the form. I think he answered your question.
THE WITNESS: I'm not aware that it's a strong association or a weak association. It's a statistically significant association.
BY MR. ZELLERS:
Q. You cannot point me to any peer-reviewed literature on talc and ovarian cancer that states that 1.3 is a strong association; correct?
MS. O'DELL: Object to the form. Asked and answered.
THE WITNESS: That's correct.
BY MR. ZELLERS:
Q. IARC does not refer to this as a strong association; correct?
A. I'm not familiar with what IARC says.
Q. FDA does not refer to this as a strong association; correct?
A. I'm not aware.
Q. The National Cancer Institute does not refer to this as a strong association; correct?
A. I'm not aware what they said about strong or

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weak.
Q. Do your opinions on causation and strength of association apply equally to all forms of ovarian cancer?
A. No.
Q. Are you able to break down your opinion with respect to ovarian cancer?
A. Yeah. So there are three types of ovarian cancer: germ cell, sex cord-stromal, and epithelial ovarian cancers. I have no evidence that sex cord-stromal tumors or germ cell tumors are associated with the use of talcum powder, although they are rare cancers, so it would take much larger populations to really fully investigate that issue.
Q. Do you -- strike that.
Does your opinion on strength of association and causation apply equally to all forms of epithelial ovarian cancer?
A. Reading the literature, it appears that there is some variation in terms of impact that talcum powder might have on some forms of ovarian cancer.
Q. Tell us what your opinions with the different subtypes of epithelial ovarian cancer and whether or not they are either a risk factor or a causative factor for ovarian cancer.

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MS. O'DELL: Object to the form.
THE WITNESS: I'm not sure that question --
BY MR. ZELLERS:
Q. I thought it was a good question. I can try to do it again, but, did you not understand that question?
A. I think what you're trying to get at is does talcum powder have equal carcinogenic effect resulting in different types of epithelial ovarian cancers?
Q. Yes.
A. Okay. So different types of epithelial ovarian cancers are separated into several -- and we believe there are several different mechanisms that cause them. So in the past, they've been lumped into epithelial ovarian cancers; but, in fact, the biology of mucinous tumors -- cancers -- are different than serous cancers.
Based on the epidemiologic evidence that I've seen, there is a preponderance of impact on women that have serous carcinomas of the ovary, which is the most common ovarian cancer; and because it is the most common, it's more likely we're going to see a statistical association as opposed to a rarer cancer like a mucinous cancer.

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So that is my answer to your question.
Q. Do your opinions as to talcum powder used in the perineal area being a risk factor and/or a causative factor for serous ovarian cancer also apply to mucinous ovarian cancer?
A. I think the association is weaker for mucinous.
Q. How about for endometrioid?
A. I think some studies have suggested endometrioid is increased risk with talcum powder.
Q. Is it weaker?
A. Is it weaker?
Q. Than serous.
A. Than serous? I'm not certain of that.
Q. Clear cell, is it weaker than serous?
A. I'm not certain of that because clear cell is a very rare cancer.
Q. On page 8 of your report, you say that (as read):
"The strength of association between talcum powder and ovarian cancer is critically important because of severity and frequency of ovarian cancer."
Is that right?

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A. That's what I say.
Q. Do you believe that ovarian cancer is a frequently occurring disease?
A. In my practice it is. It occurs in 22,400 women a year in the United States, and about 14,000 of those women will ultimately die of their cancer.
Q. What is your support for that?
A. My support for that data, the incidence of ovarian cancer?
Q. Yes.
A. Well, I may have rounded it off and it may not be exact, but the American -- I mean the American Cancer Society, the SEER database. Those would be two sources of information that count the annual incidence of ovarian cancer and the mortality from ovarian cancer.
Q. When you examine a causation, are you more likely to consider a lower association causal if the disease is severe or frequent?
MS. O'DELL: Object to the form.
THE WITNESS: Let me read your question again.
I'm not sure what you mean by "lower association."

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BY MR. ZELLERS:
Q. You have told us in your report that "the strength of association between talcum powder and ovarian cancer is critically important because of the severity and frequency of ovarian cancer."
Is that right?
A. Yes, that's right.
Q. My question is, when you examine causation, are you more likely to consider a lower association causal if the disease is severe or frequent?
MS. O'DELL: Object to the form.
THE WITNESS: No, it doesn't have anything to do with my opinion as to what the causation is.
BY MR. ZELLERS:
Q. Langseth, 2008, that is a study that you have reviewed and that you rely upon for your opinions in this case; is that right?
A. I believe so. It's one of the meta-analyses, as I recall.
Q. Are you familiar with the Langseth publication?
A. I have read it, and I think it's of value, but --
Q. Take a look at -- I'm going to hand you the

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exhibit copy.
A. Sure.
Q. We have marked this one as Exhibit 21.
(Exhibit No. 21 was marked for identification.)
THE WITNESS: Okay.
MS. O'DELL: Feel free to look at your own copy if you'd rather, Doctor.
BY MR. ZELLERS:
Q. Do you have Exhibit 21?
A. Yes. You gave me two copies. Here, let me give you one back.
Q. Ah, okay.
You have both the exhibit copy I gave you, which is not highlighted, and you have your own personal highlighted copy of the study; is that right?
A. Yes, sir.
Q. On page 7 of your report, you address this meta-analysis by Langseth; is that right?
A. I've lost track of my report, but as soon as I get to it -- here we go.
Q. Your report is Exhibit 5; is that right?
A. I have one that's not marked, but go ahead.
Q. Well, turn to page 7.
A. Mm-hmm.
Q. And do you see in your chart you have

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identified Langseth as one of the six articles that you have pulled out and highlighted in your paper; is that right?
A. Yes.
Q. And you list the odds ratio found by Langseth and the other authors in that paper to be 1.40; is that right?
A. That's correct.
Q. Go to Figure 1 on page 359 of the Langseth article, Exhibit 21.
Do you have that?
A. Yes.
Q. And Langseth lists 20 case-control studies; is that right?
A. I believe so.
Q. Of those 20 studies, only 10 have statistically significant results; is that right?
A. I'm going to have to go through each one, so give me a moment here.
I count 11.
Q. You count 11 that found a statistical significance?
A. Where the confidence interval does not overlap 1.
Q. Well, we have Cramer; correct?

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A. Yes.
Q. Second, Harlow; correct?
A. Yes.
Q. Cramer again; correct?
A. Yes.
Q. Purdie; is that right?
A. Yes.
Q. Chang?
A. Yes.
Q. Cook?
A. Yes.
Q. Green?
A. Yep.
Q. Cramer?
A. Yep.
Q. Ness?
A. Yes.
Q. Mills?
A. Yes.
Q. That's 10. You see another one?
A. Okay. I'm sorry. I counted the pooled odds ratio population-based studies. So 10. Yes, I agree with you.
Q. So out of the 20 case-control studies that are cited by Langseth and that you rely on for your

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opinions in this matter, only 10 of the 20 have statistically significant results; is that right?
A. Yes.
Q. Is this the first time that you've done that exercise, that you've actually looked at the 20 studies and determined that only 10 of them have statistically significant results?
MS. O'DELL: Object to the form.
THE WITNESS: No. I didn't go through every -- to count -- let me read your question again. I was not aware of the exact count that you brought to my attention. On the other hand, I think that this paper results in a statistically significant finding. That's the beauty of a meta-analysis.
BY MR. ZELLERS:
Q. Would you agree that 10 out of 20 is no better than a coin toss?
MS. O'DELL: Object to the form.
THE WITNESS: You're misusing epidemiologic data.
BY MR. ZELLERS:
Q. Would you agree that 10 out of 20 is no better than a coin toss?
MS. O'DELL: Object to the form.
THE WITNESS: You'll have to tell me

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what 10 out of 20 we're talking about.
MS. O'DELL: Sorry, Doctor. Object to the form. Asked and answered.
You may answer his question.
BY MR. ZELLERS:
Q. Generally, if you flip a coin 20 times, are you going to get 10 heads and 10 tails?
MS. O'DELL: Object to the form.
THE WITNESS: Statistically, yes.
BY MR. ZELLERS:
Q. All right. Is it your opinion that 10 out of 20 means there are consistent results across studies --
A. That's where a meta-analysis puts weight onto some studies more than others.
Q. The --
A. -- and comes up with a conclusion that this is a statistically significant finding, pooling all of these papers.
Q. Langseth is just looking at the case-control studies; is that right?
A. Yes.
Q. Langseth concluded -- and the authors concluded -- that causation should be rejected and that more study is needed; is that right?

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MS. O'DELL: Object to the form.
THE WITNESS: I'd have to see where that's written.
BY MR. ZELLERS:
Q. Well, look under -- so same page, underneath our table, see where it says "Proposal to research community"?
A. Yes.
Q. (As read):
"The current body of experimental and epidemiological evidence is insufficient to establish a causal association between perineal use of talc and ovarian cancer risk."
Did I read that correctly?
A. You read that correctly.
Q. Would you agree that you're drawing conclusions from this study that are broader than the study authors' own conclusions?
MS. O'DELL: Object to the form.
THE WITNESS: My opinion is not based on just this study; it's based on all of the studies that I have in my report where there's a consistency across all meta-analyses that there's a statistically increased risk of ovarian cancer in women exposed to

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perineal talc. Those confidence intervals in all of those meta-analyses are statistically significant.
MR. ZELLERS: Move to strike as nonresponsive.
BY MR. ZELLERS
Q. Are these -- at least with the Langseth paper, you've gone further than what the authors have concluded; correct?
MS. O'DELL: Object to the form.
THE WITNESS: I'm developing my opinion on the totality of the evidence that I have reviewed.
BY MR. ZELLERS:
Q. Please answer my question. Just on the Langseth paper --
A. My opinion is not based on the Langseth paper.
Q. I understand. But with respect to Langseth and the opinions that you've drawn from Langseth, you've gone further in your conclusions than the Langseth paper authors; correct?
A. No, I do not.
MS. O'DELL: Excuse me.
Object to the form. Misstates his testimony.
You may repeat your answer if you'd like.

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THE WITNESS: My conclusions are not based on only Langseth. That is a piece of information that I've used in formulating my opinion.
BY MR. ZELLERS:
Q. Consistency is one of the Bradford Hill factors; is that right?
A. Yes, sir.
Q. On page 6 of your report, you discuss the epidemiological studies on talcum powder and ovarian cancer; is that right?
A. Yes.
Q. In the second paragraph, under "Epidemiology," you state (as read):
"When looking at these epidemiologic studies and their totality, the data shows a consistent statistically significant increased risk of developing EOC [epithelial ovarian cancer] with perineal talcum powder use."
Is that right?
A. Yes, sir.
Q. In looking at this section, you don't discuss or address the cohort studies at all; is that right?

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A. That's right.
Q. You just discuss the case-control studies and then the meta-analyses; is that right?
A. That's correct.
MS. O'DELL: Object to the form.
BY MR. ZELLERS
Q. The cohort studies do not show a statistically significant association between talc use and ovarian cancer; is that right?
A. The cohort studies were not designed to answer that question. They're poorly done and I don't think contribute to this discussion.
Q. Is that a "yes," that the cohort studies do not show a statistically significant association between talc use and ovarian cancer?
A. The way they're written and studied and reported, you're correct.
Q. Berge 2017, that's a paper you've got in one of your folders that we went through earlier today. And you're generally familiar with that study; is that right?
A. Yes.
Q. In Berge, the authors concluded that (as read):
"The positive association between

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talc use and ovarian cancer appears to be limited to serous histologic type and to case-control studies."
Do you agree with that?
A. Yes.
Q. How can you validate completely excluding cohort studies from your discussion?
MS. O'DELL: Object to the form.
THE WITNESS: Because I don't think they contribute one way or the other. They're poorly designed, poorly executed, and the data that they provide does not inform us at all.
And, in fact, these meta-analyses, in many cases, included the cohort studies and still came out with statistically significant increased risk of ovarian cancer.
BY MR. ZELLERS:
Q. It was appropriate for you to exclude the cohort studies from your discussion; correct?
MS. O'DELL: Object --
THE WITNESS: I did --
MS. O'DELL: Excuse me. Object to the form. Misstates his testimony.
You may answer.

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THE WITNESS: This table back here that's got all these papers on it, we excluded. They're not in my discussion. I considered them, and I didn't think that they contributed to the information that I needed to present in my report.
BY MR. ZELLERS:
Q. You state that Penninkilampi shows that the cohort studies support a statistically -- well, strike that.
I want to ask you a few questions about the cohort studies.
Did you review the Gates 2010 cohort study?
A. Yes.
Q. The Gates 2010 cohort study found that there was not a statistically significant relationship for the serous invasive subtype of ovarian cancer; is that right?
A. I believe that's true, from my recollection.
Q. Berge 2017 shows that the cohort studies do not support a statistically significant relationship between perineal talc use and ovarian cancer for any subtype; is that right?
MS. O'DELL: Object to the form.
THE WITNESS: This is Berge's analysis of the cohort studies and Berge's meta-analysis. Is

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that the paper you're talking about?
BY MR. ZELLERS:
Q. Yes. 2017.
A. I presume, if you're reading it, that's what he says.
Q. Well, I'm looking at Berge 2017, page 6, left column, at the bottom (as read):
"This positive association appears to be limited to serous histologic type and the case-control studies."
We covered that earlier; correct?
A. Yes.
MS. O'DELL: What page, please?
MR. ZELLERS: Page 6.
BY MR. ZELLERS:
Q. We're in agreement on that; correct, Doctor?
MS. O'DELL: Object to the form. Give him a moment.
THE WITNESS: Yes, he says that in his abstract.
BY MR. ZELLERS:
Q. You were aware that Berge 2017 included the Gates 2010 cohort study; is that right?
A. Yes. It's in Figure 2.

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Q. You're aware that one of the studies -- another one of the meta-analyses that you cite to, Penninkilampi 2018, excludes the Gates 2010 cohort study; right?
A. I believe so.
Q. How did you make a determination to weigh Penninkilampi more heavily than Berge?
They're both meta-analyses; correct?
A. Right.
Q. Why did you make a determination to weigh Penninkilampi 2018 and place greater weight on it than the Berge study?
MS. O'DELL: Object to the form.
THE WITNESS: I don't think I necessarily placed greater weight on it. I've told you how I weight studies, and they all contribute to the totality of my opinion.
BY MR. ZELLERS:
Q. Did you -- well, strike that.
Isn't it a problem that Penninkilampi 2018 does not factor in the data from the Gates 2010 study, given that the Gates study tends to negate an association between perineal talc use and ovarian cancer?
MS. O'DELL: Object to the form.

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THE WITNESS: I can't explain to you what Penninkilampi was thinking or why he chose to exclude it.
BY MR. ZELLERS:
Q. Did you verify that the data that Penninkilampi reports is accurate?
A. Have I gone through every single case-control study and verified every number that's in his tables?
Q. Have you -- strike that.
Penninkilampi purports to report odds ratios, lower limits and upper limits, for the individual studies; is that right?
A. Yes.
Q. Did you go back to verify that Penninkilampi was correct in his reporting of the results of those individual studies?
A. Yeah, that's the question I was just asking you.
No, I did not go back.
Q. In determining the study is of high quality, would it be important to you that the authors are accurately reporting the odds ratios and the confidence intervals?
MS. O'DELL: Object to the form.
THE WITNESS: I trust the peer review

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process that resulted in this publication.
BY MR. ZELLERS:
Q. If there were errors in reporting of the odds ratios or the confidence intervals, would that call into question the reliability of the study?
MS. O'DELL: Object to the form.
THE WITNESS: It might.
BY MR. ZELLERS:
Q. Of the histological subtypes for epithelial ovarian cancer, do you consider endometrioid and clear cell to be related?
A. No.
Q. You do not consider endometrioid and clear cell ovarian cancer to be related?
A. Only related in they fall into the classification of epithelial ovarian cancers.
Q. Penninkilampi only found a statistically significant increased risk for serous and endometrioid ovarian cancers; is that right?
A. Okay. Yes.
MS. O'DELL: Let -- excuse me, Doctor. If you need to look at the --
BY MR. ZELLERS:
Q. You have Penninkilampi in front of you, right, Doctor?

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A. I have.
Q. And if you need to take any more time to answer any of my questions, please do.
A. Okay.
Q. Penninkilampi did not find a statistically significant increased risk for clear cell or mucinous ovarian cancer; is that right?
A. Can you show me where you're reading it from?
Q. Sure. Take a look at the abstract for the results.
A. He says he found an increased risk of serous and endometrioid but not mucinous or clear cell.
Q. And that's where I was going to. So our record is complete, let's mark -- well, let's mark both Berge 2017 -- we'll mark Berge 2017.
MS. O'DELL: Mike, I think there's an updated Berge publication, 2018. Do you have the most up to date?
MR. ZELLERS: Asking him a question about the Berge publication copyrighted 2017 that appeared in "Genital Use of Talc and Risk of Ovarian Cancer, a Meta-analysis." That's the one that I'm referring to and I believe the one that the doctor has identified in his materials.
THE WITNESS: Actually, mine is from

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May of 2018, European Journal of Cancer Prevention.
BY MR. ZELLERS:
Q. Okay. So let's do this: Doctor, if you don't mind, hand me your copy. We'll mark that as Deposition Exhibit 23.
MR. ZELLERS: For right now, I'm going to just put a No. 23. And, Ms. Court Reporter, if, at a break, you can put an official sticker on it.
MS. O'DELL: I hate to even say this, but did we mark 22?
MR. ZELLERS: Yes. So Deposition Exhibit 22 is the Berge 2017 paper.
Deposition Exhibit 23 is the Berge publication that appeared in the European Journal of Cancer Prevention, dated May 2018.
(Exhibit Nos. 22 and 23 were marked for identification.)
BY MR. ZELLERS:
Q. So I'm going to hand both of these back to you, Dr. Clarke-Pearson.
MR. ZELLERS: I'm going to hand out my exhibit copies to counsel.
Let me also, just so we have it in the record, we'll mark as Deposition Exhibit 24 the Penninkilampi meta-analysis that's referred to in the

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doctor's report.
(Exhibit No. 24 was marked for identification.)
BY MR. ZELLERS:
Q. All right, Doctor. Can I ask you some more questions?
A. Let's go for it.
Q. Does it make sense that an environmental exposure could increase the risk for endometrioid ovarian cancer but not clear cell ovarian cancer?
MS. O'DELL: Object to the form.
THE WITNESS: Yes.
BY MR. ZELLERS:
Q. How do you explain that finding?
A. Well, we've talked about mutations previously, and I'll bring it up again, that different mutations occur that result in different types of cancers. And so the ovarian epithelium being exposed to talcum powder may develop different cancers, depending upon the impact that that talcum powder and its products have on that particular cell.
Q. Do you believe -- and, I think, as you told us earlier -- that you find a stronger association between perineal talcum powder use and serous ovarian cancer than you find for endometrioid, clear cell, or mucinous ovarian cancer; is that right?

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MS. O'DELL: Object to the form.
THE WITNESS: I think serous has the strongest association. But in some studies we see, just as you're quoting from the -- whichever the study is that we're looking at, that endometrioid -- the Penninkilampi study -- so serous and endometrioid is increased.
BY MR. ZELLERS:
Q. But not clear cell or mucinous; correct?
A. That's correct in this one study.
Q. Do you believe that Penninkilampi 2018 provides evidence that there's a biologically plausible mechanism by which talc can cause ovarian cancer?
A. I don't recall, and I'm not seeing it as I do a quick scan, that he addresses mechanisms of cancer -- carcinogenesis. I wouldn't expect that in an epidemiologic study.
Q. Penninkilampi specifically states that (as read):
"A certain causal link between talc use and ovarian cancer has not been established."
Correct?
MS. O'DELL: Object to the form.

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THE WITNESS: That's what he has written, and you've read it correctly.
MS. O'DELL: Are you reading at a certain page, Counsel?
MR. ZELLERS: Yes. I was reading from page 42, the end of the first paragraph.
THE WITNESS: Okay. Right.
BY MR. ZELLERS:
Q. Did I read that correctly? It's the last statement in the first paragraph in the left-hand side (as read):
"A certain causal link between talc use and ovarian cancer has not yet been established."
Did I read that correctly?
A. I'm sorry. I'm losing track of where you are. Are you up here?
Q. Right here (indicating).
A. Okay. Yes, you read it correctly.
Q. Cohort studies are not affected by recall bias; is that right?
A. Not by recall bias, no.
Q. All of the cohort studies were prospective as opposed to retrospective; is that right?
A. The cohort studies gathered information about

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exposure at one point in time and never followed the patients subsequent to that to get some idea of frequency of use, whether the patient continued to use the talcum powder so that the real question is ever use. We don't know duration and frequency from these cohort.
MR. ZELLERS: Move to strike as nonresponsive.
MS. O'DELL: Oppose the motion.
MR. ZELLERS: And, Counsel, I understand that anytime I do that, you will oppose it.
MS. O'DELL: I just wanted to make it clear. Didn't want you to think I was asleep over here.
MR. ZELLERS: I'm going to ask my question again.
BY MR. ZELLERS:
Q. Dr. Clarke-Pearson, all of the cohort studies were prospective as opposed to retrospective; correct?
A. They're prospective except for the fact that they don't continue to evaluate the ongoing use of talc in these patients. It was a point in time that the patient was asked whether she did or didn't use talc.

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Q. The cohort studies were not subject to the same selection bias as retrospective case-control studies; is that right?
A. That's true.
Q. Recall bias is a concern in every retrospective study; correct?
A. Yes.
Q. Recall bias can distort a scientific evaluation of whether an exposure is actually related to a disease; correct?
MS. O'DELL: Object to the form.
THE WITNESS: Let me read your question again.
Recall bias has that risk of not being able to analyze the data.
BY MR. ZELLERS:
Q. For example, recall bias could distort results if women with ovarian cancer were more likely to remember their exposure to talc than women without ovarian cancer; is that right?
MS. O'DELL: Object to the form.
THE WITNESS: The issue in these large case-control trials is that we have many, many more women in them that have ovarian cancer. And, therefore, those potentially confounding factors get

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worked out in most cases, and there is a consistency across all of these studies.
BY MR. ZELLERS:
Q. I'm going to ask you about consistency. I'm going to ask you about confounding factors. But, for right now, please try to answer my question.
Recall bias could distort results if women with ovarian cancer were more likely to remember their exposure to talc than women without ovarian cancer; correct?
A. Yes, that could distort the results.
Q. Recall bias could explain the fact that some retrospective case-control studies have found a statistically significant relationship between talcum powder and ovarian cancer but the cohort studies have not; correct?
MS. O'DELL: Object to the form.
THE WITNESS: (As read):
"Recall bias could explain the fact that some retrospective case-control studies have found a statistically significant relationship between talcum powder and ovarian cancer?"
Yes, that's true.

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And then you go on to say "but the cohort studies have not."
Have not found a statistically significant relationship? That's true. The cohort studies haven't found a statistically -- because the cohort studies have many other confounding and inadequate parts of their evaluation.
MR. ZELLERS: Move to strike as nonresponsive.
BY MR. ZELLERS:
Q. You rely on the Schildkraut case-control 2016 study for your opinions about dose response; is that right?
A. About what response?
Q. About dose response.
A. Dose response? That's one of the studies.
Q. All right. Take a look, if you will, please, at Deposition Exhibit 25, which is the Schildkraut 2016 study cited and relied upon by you.
(Exhibit No. 25 was marked for identification.)
BY MR. ZELLERS:
Q. Do you have that in front of you?
A. Yes. You just handed it to me.
Q. And this is a study that you have previously reviewed and you cite to in your materials in this

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case; is that right?
A. Yes.
Q. Schildkraut 2016 looked at, among other things, what impact, if any, lawsuit filings in 2014 had had on whether women recalled using talc in the past; is that right?
A. I think she tried to evaluate that, yes.
Q. The authors thought that the publicity from the lawsuits might influence the participants' recall of prior body powder use; is that right?
A. Yes.
Q. If we go to page 4 of Exhibit 25 --
A. Page 1414, Table 2?
Q. Yeah. Page 1414, Table 2, the second column shows the number of cases. That's women with ovarian cancer; is that right?
A. Yes.
Q. The third column shows the controls. Those are the women who do not have ovarian cancer; is that right?
A. That's correct.
Q. Looking at this data, before 2014, before the lawsuits, the percentage of controls -- meaning women without ovarian cancer -- who said they used talc on their genitals was 34 percent; is that right?

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A. That's not in this table, I don't think, is it?
Q. Take a look -- do you see, under "Exposure," "Body powder use by location"? It's about eight lines down, "Interview date, less than or earlier than 2014."
A. I'm with you, yeah. Okay.
Q. All right. So the percentage of controls -- meaning women without ovarian cancer -- who said they used talc on their genitals was 34 percent; is that right?
A. I'm not seeing that. I see "interview date less than 2014, never used."
Q. Then you go down to "any genital use."
A. Okay. "Any genital use, 34 percent," yes. I see what you're saying.
Q. And then the percentage of cases -- meaning women with ovarian cancer -- that they said used talc on their genitals who were interviewed before 2014 was 36.5 percent; is that right?
A. Right. That's correct.
Q. So roughly the same reporting of genital talc use between women with and without ovarian cancer before the lawsuits were filed; is that right?
A. Yes.

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Q. Now, look at what happened after the lawsuits were filed.
A. I see.
Q. After 2014, what percent of women without ovarian cancer said they used talc on their genitals?
A. 34.4 percent.
Q. So essentially the same as before; is that right?
A. Yes.
Q. So, based on this data, the lawsuits had essentially no effect on how many of the women without ovarian cancer, the controls, remembered or recalled using baby powder; is that right?
A. That seems to be true.
Q. For women with ovarian cancer, as we discussed, before the lawsuits were filed, 36.5 percent of them said they recalled using baby powder; is that right?
A. Yes.
Q. But after the lawsuits were filed, the percent of women with ovarian cancer who said they used baby powder went up to 51.5 percent; is that right?
A. That's correct.
Q. So after the lawsuits were filed, the percent

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of women with ovarian cancer who said they used baby powder jumped by over 40 percent; is that right?
A. It went from 36.5 to 51.5.
Q. That's just over 40 percent; correct? That increase?
A. From 36 to 51?
Q. Yes.
A. You're doing the math, but --
Q. Well, it's a substantial increase.
A. Yes.
Q. Would you agree with that?
MS. O'DELL: Object to the form.
THE WITNESS: Yes.
BY MR. ZELLERS:
Q. All right. So, looking at this data, lawsuit filings affected how many women with ovarian cancer remembered using talc on their genitals but basically had no effect on the memory of women without ovarian cancer; correct?
MS. O'DELL: Object to the form.
THE WITNESS: I don't know that it -- the hypothesis that Dr. Schildkraut puts out there is that the lawsuit filings may have changed women's recall, if you will. There may be other factors that are involved here too.

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BY MR. ZELLERS:
Q. At least according to the author, the women, after a lawsuit was filed, with ovarian cancer remembered using talc much more than the women without ovarian cancer; correct?
A. Yes.
MS. O'DELL: Object to the form.
BY MR. ZELLERS:
Q. Those findings would be an example of the potential effect of recall bias; is that right?
A. Yes.
MS. O'DELL: Object to the form.
BY MR. ZELLERS:
Q. What was your methodology for discounting the effect of recall bias in the population-based case-control studies?
A. My methodology was to rely on a skilled epidemiologist like Dr. Schildkraut to work her way through all of the data and come up to her conclusions.
Q. Is there a rate of error in such a methodology?
MS. O'DELL: Object to the form.
THE WITNESS: I'm not sure I know what you mean by "rate of error."

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BY MR. ZELLERS:
Q. Didn't the cohort studies involve a much greater number of women than the case-control studies?
A. More women altogether, but less cancer cases.
Q. What was your methodology for weighing the power of the cohort of studies versus the case-control studies?
A. My methodology was to look at the issues regarding cohort studies that are at fault, that are defective in their trial design and the reporting of their data.
Q. You're speaking about cohort studies in general; is that right?
A. Well, three cohort studies.
Q. Is that right? But you're talking about the studies in general as opposed to specific aspects of the individual cohort studies?
A. We can go through the specifics of these three studies.
Q. Well, Gates 2010, the Nurses' Health Study, did you review that?
A. Yes.
Q. It was a follow-up to the cohort study Gertig 2000; is that right?
A. Yes.

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Q. It's an analysis of data collected in the Nurses' Health Study; correct?
A. Yes.
Q. The analysis included over 100,000 women; is that right?
A. I believe so.
Q. The women in the Nurses' Health Study were followed from 1976 to 2006, so for 30 years; is that right?
A. The knowledge in this study by the study -- the researchers doing the study did not gain any information about exposure until 1982.
Q. After following over 100,000 women for three decades, the data did not show a statistically significant relationship between talcum powder use and any type of epithelial ovarian cancer; is that correct?
MS. O'DELL: Object to the form.
THE WITNESS: That's correct, and there's many defects in the design of this study.
For example, the patients were never asked, once again after 1982, whether they used or didn't use talc or how frequently they used talc.
BY MR. ZELLERS:
Q. Well, let me ask you questions about that.

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The Nurses' Health Study participants were between the ages of 30 to 55 at the start of the study in 1976; is that right?
A. I believe so.
MS. O'DELL: If you need to see it --
THE WITNESS: I don't have -- well, maybe I do have it here.
BY MR. ZELLERS:
Q. If you need to take a look at it -- do you have it in front of you? I can give it to you if you need it.
A. Okay.
Q. So my question is the Nurses' Health Study participants were between the ages of 30 to 55 at the start of the study in 1976; is that right?
A. Yes.
Q. They were asked about their talcum powder use in 1982; is that right?
A. That's my understanding, yes.
Q. So they would have been between the ages of 36 and 61 when they were asked about their talcum powder use; is that right?
A. Yes.
Q. Most women, as we have discussed, who used talc in their perineal region start that use before

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age 30; right?
A. That's what we've seen in other studies.
Q. So if a study asks women ages 36 to 61 if they use talcum powder, it would capture the majority of women who use genital powder during the follow-up period; correct?
MS. O'DELL: Objection to form.
THE WITNESS: During the follow-up period?
BY MR. ZELLERS:
Q. Yes.
A. No. It's a point in time. The question was ever used up to 1982.
Q. It would capture the majority of women who use, genital powder use; is that right? In this study.
MS. O'DELL: Object to the form.
THE WITNESS: Up till 1982.
BY MR. ZELLERS:
Q. Houghton, 2014, the Women's Health Initiative Study, did you review that study?
A. I did.
Q. That study involves over 61,000 women; is that right?
A. And only 429 cases of ovarian cancer.

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Q. Houghton 2014 did not find a statistically significant relationship between perineal talc use and ovarian cancer among women who had ever used talc; is that right?
A. Yes. And this study was not powered to identify --
MS. O'DELL: If you need it.
THE WITNESS: -- the relative risk that we're talking about in the cohort studies -- I mean the case-control studies. Excuse me.
BY MR. ZELLERS:
Q. Or among women who had fewer than nine years of perineal talc use; right?
A. That's what I believe.
Q. I'm looking at page 4, Houghton 2014, Table 2.
A. Okay. The question again? Table 2?
Q. Yeah. The question is Houghton did not find a statistically significant relationship between perineal talc use and ovarian cancer among women who had fewer than nine years of perineal talc use; right?
A. Yes. That sort of exposure is minimal.
Q. Or among women who had more than ten years of perineal talc use; is that right?
A. Yes.

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Q. And the same results for talcum powder on a sanitary napkins or diaphragms; is that right?
A. Yes.
Q. Isn't it true that, when combined in a meta-analysis, these cohort studies, the three that we're talking about, have sufficient power to detect a relative risk of 1.25?
A. I'm not aware that that -- how that calculation was made.
Q. Did you consider the published power calculation by Berge?
And so if you look at the Berge 2017 paper, page 6, second column, first paragraph, Berge and his coauthor states (as read):
"The statistical power of the meta-analysis of these cohort studies" --
MS. O'DELL: I'm sorry, Mike. Where are you reading? Page 6?
MR. ZELLERS: Page 6, second column, first paragraph.
MS. O'DELL: Thank you.
MR. ZELLERS: Sure.
THE WITNESS: Second column. That's what this looks like to me (indicating).

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BY MR. ZELLERS:
Q. Looking at Exhibit 22.
A. I've got 23, which is the more recent paper.
Q. Well, take a look at 22, which is the year before, 2017. And I'm looking at page 6. And I'm looking at the last part of the first full paragraph in the right-hand column.
Are you with me?
A. "The important feature of the present meta-analysis"?
Q. Yes.
A. Okay.
Q. And so if we go down about two-thirds of the way, Berge and the authors conclude (as read):
"The statistical power of the meta-analysis of these cohort studies to detect a relative risk of 1.25, similar to the result of the meta-analysis of case-control studies, was 0.99. Thus low power of cohort studies cannot be invoked as an explanation of the heterogeneity of results."
Do you see that?
A. Let me read it one more time, please.

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Q. Sure.
A. So he is saying that the cohort studies are not powered to detect 1.25.
Q. What he is saying, I believe, is that the cohort studies are powered to detect a relative risk of 1.25, which was the basis for his conclusion in the last sentence (as read):
"Thus low power of cohort studies cannot be invoked as explanation of the heterogeneity of results."
MS. O'DELL: Object to the form.
THE WITNESS: I read that with a different understanding.
What he's saying is that the ability of the cohort study is to detect a relative risk of 1.25 that is similar to the results of the meta-analyses case-control studies was only .99.
So those cohort studies aren't powered to detect 1.25.
BY MR. ZELLERS:
Q. Does Berge conclude "Thus low power of cohort studies cannot be invoked as explanation of the heterogeneity of results"?
A. And I'm not sure what I mean -- what you mean by -- what he means by "heterogeneity of results."

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Q. Did I read it correctly?
A. Yes, you read it correctly.
Q. All right.
You're familiar with the hospital-based case-control studies; is that right?
A. They are part of the case-control studies, yes.
Q. You agree with me that none of the hospital-based case-control studies show a statistically significant association between talc use and ovarian cancer; is that right?
MS. O'DELL: Object to the form.
THE WITNESS: I would have to go back to each one of those studies, sir.
BY MR. ZELLERS:
Q. Well, let's -- do you have Langseth there? That might be an easy way to --
A. I do.
Q. -- take a look at this.
We looked at the Langseth as Deposition Exhibit 21.
A. I have it.
Q. And if we look at his table on page 359, he lists out each of the hospital-based case-control studies.

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Do you see that?
A. Right. Those are in the forest plot, yes.
Q. None of the hospital-based case-control studies show a statistically significant association between talc use and ovarian cancer; correct?
A. Yes.
Q. The results of the hospital-based case-control studies are not consistent with the results of the population-based case-control studies; correct?
A. That's right. That's why they're combined.
Q. What methodology did you use to account for this lack of consistency between the population-based case-control studies and the hospital-based case-control studies?
A. This is what the beauty of a meta-analysis is, where it brings together all the studies and comes to a conclusion. And the conclusion here is that there's a 1.35 risk of developing ovarian cancer in women who receive perineal talc.
Q. Which Langseth and the other authors concluded was "insufficient to establish a causal association between perineal use of talc and ovarian cancer risk"; correct?
MS. O'DELL: Object to the form.

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THE WITNESS: It's statistically significant, which to a clinician means that we could reduce the risk of ovarian cancer if we eliminated talcum powder from the patients that are being exposed to it.
MS. BOCKUS: Object. Nonresponsive.
MR. ZELLERS: Joined.
BY MR. ZELLERS:
Q. Are you familiar with the term "selection bias"?
A. Yes.
Q. What does "selection bias" mean?
A. Means that the selection of the patients in a particular study may be inappropriate, that they may not be the proper controls or the proper candidates to be included in the study.
Q. You agree that hospital-based case-control studies may be less susceptible to selection bias than population-based case-control studies; correct?
MS. O'DELL: Object to the form.
THE WITNESS: I'm not sure I believe that.
BY MR. ZELLERS:
Q. Well, hospital-based case-control studies, you're more likely to be comparing hospitalized

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patients to hospitalized patients; is that right?
A. Yes.
Q. Whereas in a population-based study, you're more likely to be comparing ill people to healthy people; is that right?
MS. O'DELL: Object to the form.
THE WITNESS: In a hospital-based study, the people are ill. That's why they're in the hospital.
BY MR. ZELLERS:
Q. And they're compared to other ill people, other hospitalized patients; is that right?
A. Yes.
Q. There's a difference in the populations that are being studied between a hospital-based case-control study and a population-based case-control study; correct?
A. Yes.
Q. How did you account for selection bias in population case-control studies?
A. I think if there was selection bias -- and I didn't control for selection bias, but if there was selection bias, first of all, it would be usually negated by the large number of patients in that study.
Q. Even among the population-based case

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controls, some studies have shown statistically significant findings and some have not; is that right?
A. Yes.
Q. What is your methodology for weighing the lack of consistency in statistical significance across case-control studies?
MS. O'DELL: Objection to form.
THE WITNESS: That's where a meta-analysis becomes a very valuable tool.
BY MR. ZELLERS:
Q. You agree that, if a study does not show a statistically significant association, it could mean that no risk exists; is that right?
A. It's a possibility, yes.
MS. O'DELL: Excuse me, Mike. When you get to a -- we've been going an hour and 45 minutes or so.
MR. ZELLERS: Let's take a break.
THE VIDEOGRAPHER: Going off the record at 12:46 p.m.
(Recess taken from 12:46 p.m. to 1:45 p.m.)
THE VIDEOGRAPHER: Back on record at 1:45 p.m.
BY MR. ZELLERS:
Q. Dr. Clarke-Pearson, in your report, page 7,

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you have a table where you state that you reviewed six meta-analyses reported between 1995 and 2018; is that right?
A. Yes. I overlooked adding Berge to this list.
Q. What other studies did you overlook adding to this list?
A. Subsequent to my report, there's also a meta-analysis by Taher.
Q. Any other studies that you omitted from your report and specifically the table on page 7?
MS. O'DELL: Object to the form.
THE WITNESS: No, not that I'm aware of.
BY MR. ZELLERS:
Q. What's the difference -- well, strike that.
In your report, page 7, you list out five meta-analyses and a pooled analysis; is that right?
A. Yes.
Q. What is the difference between a pooled analysis and a meta-analysis?
A. You know, I really can't give you a good definition of that.
Q. How did you select these five studies to set forth in your report?
A. I think these were all of the meta-analyses

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that I was aware of.
Q. Did you only review the studies that showed a statistically significant relationship between perineal talc use and ovarian cancer?
A. I believe I included all the meta-analyses that I could identify.
Q. Meta-analyses and pooled analyses combine the work of other published studies into one study; is that right?
A. Yes.
Q. If there are biases and confounding in the underlying studies, the meta-analysis or pooled analysis will reflect the biases and confounding; correct?
MS. O'DELL: Object to the form.
THE WITNESS: It obviously varies from one study to another. I would be very surprised if all studies included in the meta-analysis had the same errors, if you will.
BY MR. ZELLERS:
Q. Well, can you answer that question?
If there are biases and confounding in the underlying studies, the meta-analysis or pooled analysis will reflect the biases and confounding; correct?

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MS. O'DELL: Object to the form.
THE WITNESS: To some degree.
BY MR. ZELLERS:
Q. A proper meta-analysis or pooled analysis must analyze the sources of heterogeneity across the studies; right?
A. Yes.
Q. And a proper meta-analysis or pooled analysis must examine the methodology that lead to the underlying studies; right?
A. Yes. I think that's where the weighting done in the meta-analysis helps.
Q. Did you examine the methodology in the studies underlying these meta-analyses and pooled analyses?
A. Not in detail.
Q. Do you agree that consistency exists when different studies look at different populations -- strike that. Let me ask that question again.
Do you agree that consistency exists when different studies looking at different populations reach consistent results?
MS. O'DELL: Object to the form.
THE WITNESS: Yes. It seems to be what I would consider consistency.

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BY MR. ZELLERS:
Q. A meta-analysis does not demonstrate whether similar results were replicated across different populations; correct?
A. Yes. It combines all the papers that were considered in the meta-analysis.
Q. It combines study results into one risk calculation; is that right?
A. After weighting the different studies in terms of the number of patients and the statistics.
Q. Therefore, meta-analyses themselves cannot demonstrate consistency of results across different populations; correct?
MS. O'DELL: Object to the form.
THE WITNESS: They could demonstrate consistency.
BY MR. ZELLERS:
Q. How could they demonstrate consistency of results across different populations if what they're doing is combining the study results into one risk calculation?
MS. O'DELL: Object to the form.
THE WITNESS: I don't understand what you mean by them not being able to demonstrate consistency across different populations.

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BY MR. ZELLERS:
Q. In your report, you claim that Penninkilampi and every meta-analysis before 2018 report a similar increase in the risk of epithelial ovarian cancer with the use of talcum powder; is that right?
A. Yes.
Q. But each of these meta-analyses that you set forth on page 7 of your report use many of the same studies as the other meta-analyses; is that right?
A. Yes. Over time, new case-control studies were added to the meta-analyses.
Q. Well, for instance, Langseth 2008 and Graham 1999 each include all nine of the studies that were included in Gross and Berg 1995; is that right?
MS. O'DELL: Object to the form.
THE WITNESS: I believe --
MS. O'DELL: Did you say Graham '99?
MR. ZELLERS: No, I said Cramer '99.
MS. O'DELL: Okay. I thought you said Graham.
THE WITNESS: It says Graham on the transcription.
MS. O'DELL: So Cramer is what you're referring to, '99?
MR. ZELLERS: Yes. I'll ask that

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question again if it was unclear.
BY MR. ZELLERS:
Q. For instance, Langseth 2008 and Cramer 1999 each included all nine of the studies that were included in Gross and Berg 1995; correct?
A. I believe so.
Q. Langseth 2008 included all but one of the 14 studies that were included in Cramer 1999; correct?
MS. O'DELL: And if you need to compare --
THE WITNESS: I need to see the paper. I have Langseth; if I can see Cramer's.
BY MR. ZELLERS:
Q. Well, did you consider this in terms of analyzing the information and data?
A. No.
Q. Take a look, then, if you need to, at the Cramer 1999 paper.
MS. O'DELL: Just a moment. I'm sorry.
BY MR. ZELLERS:
Q. We're still just looking at your folders from earlier today that you have in front of you; right, Doctor?
A. Yes.
Q. Let me phrase it a different way, and then we

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can let the record -- correct this later if need be.
Doctor --
MS. O'DELL: I'll have it in front of you in one moment, Doctor.
BY MR. ZELLERS:
Q. Okay. Dr. Clarke-Pearson, you now have Langseth 2008 and Cramer 1999 in front of you; is that right?
A. Yes.
Q. Langseth 2008 included all but one of the 14 studies that were included in Cramer 1999; is that right?
A. This is the Cramer case-control study.
Q. Let me ask you the question this way, Doctor: Do you have any reason to doubt as you sit here or dispute as you sit here that Langseth 2008 did not include all but one of the 14 studies that were included in Cramer 1999?
A. I would accept that as the truth.
Q. Thank you. As you sit here, do you have any reason to doubt or dispute that Langseth 2008 included all but one of the 15 studies that were included in Huncharek 2003?
I understand you don't have the studies in front of you to be able to make that --

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MS. O'DELL: Let me just -- I would just object to the line of questions. If you're going to ask the specific studies that are listed in the table and ask him to compare --
MR. ZELLERS: No. What I'm asking him, Counsel --
MS. O'DELL: Let me finish.
It's unfair to ask him to make comparisons regarding the studies included in the meta-analyses without affording him the opportunity to look at the articles themselves.
MR. ZELLERS: And, Counsel, as you know, we've got limited time, and I don't want to sit here --
MS. O'DELL: It's still an unfair question.
MR. ZELLERS: It is not an unfair question to ask this witness if he has any reason as he sits here to dispute or to doubt that Langseth 2008 included all but one of the 15 studies that were included in Huncharek 2003.
MS. O'DELL: Well, that's not a fair question when you're not providing him an opportunity to compare the two.
And so if Dr. Clarke-Pearson wants to see a

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copy of the study, then we'll put it in front of him, because that's not a fair analysis, particularly when you're talking about multiple -- more than 10 to 15 meta-analyses -- excuse me -- cohorts over time.

MR. ZELLERS: Counsel, I've asked you a number of times not to make speaking objections. All that I am doing is asking the doctor questions about the studies included in the six meta-analyses and pooled analysis that he sets out in a chart.

If he doesn't have the answer, my question is framed as to whether or not he has any reason to dispute or doubt the overlap of studies.

MS. O'DELL: Well, I would just say, Dr. Clarke-Pearson, to the degree you remember, you can answer his questions. But, to the degree he asks you to assume something, don't assume that what counsel is stating is correct because it may or may not be true.

MR. ZELLERS: And I'm not asking the doctor to assume.

MS. O'DELL: Yes, you did.

MR. ZELLERS: I did not ask him to assume, Counsel. You can go back and read the question, but it did not ask him to assume that. It asked him if he was aware of there being any

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difference in terms of Langseth including all but one of the 15 studies that were included in Huncharek 2003.

MS. O'DELL: I stand corrected. You said "Do you have any reason to doubt or dispute," which I took to be --

MR. ZELLERS: "Do you have any reason to" --

MS. O'DELL: -- which I took to be assume.

And I'm asking you to assume that counsel is not being accurate.

BY MR. ZELLERS:

Q. Can you answer my question, Doctor?

And here's my question: Do you have any reason to believe that Langseth 2008, which you cite, included all but one of the 15 studies that were included in Huncharek 2003, which you cite?

A. Without reading and going through the table of the 'teen or so studies, I would have to assume that you're representing properly what --

Q. That is not a comparison that you have made personally; correct?

A. I have not. And if I did, I can't remember now.

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Q. Okay.

A. I mean, if this is a quiz about memorizing details of clinical studies, then...

Q. I don't want it to be a quiz. Let me ask you a new question.

If the meta-analyses are all combining the same set of studies, you would expect them to yield similar results; correct?

A. If they only contain the same set of studies but each one had slightly different, and the more recent ones added studies to them.

Q. Have you attempted to quantify how much talcum powder reaches a woman's ovaries when they use a talcum powder product?

A. Have I done some experiment?

Q. Yes.

A. I know that talcum powder gets there; I have not done any experimentation to that question.

Q. Do you have any -- were you finished?

A. Yes.

MS. BOCKUS: Object as nonresponsive.

BY MR. ZELLERS:

Q. Do you have any idea how much talcum powder reaches a woman's ovaries each time she uses it?

A. I'm sure it varies depending upon the

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menstrual cycle, the age of the patient, the patient's anatomy.

Q. It's fair to say you don't know and have not done any type of calculation or experiment to determine the answer to that question; correct?

MS. O'DELL: Object to the form.

THE WITNESS: That's correct.

BY MR. ZELLERS:

Q. Isn't the biological mechanism dependent on how much talc a woman's ovaries are exposed to?

A. Which biological mechanism are you talking about?

Q. Dose response.

MS. O'DELL: Object to the form.

THE WITNESS: So, then, rephrasing your question, isn't the dose response dependent upon how much talc a woman's ovaries are exposed to?

BY MR. ZELLERS:

Q. I'll accept that.

A. That sounds like the answer -- you answered your own question.

Q. Well, I need you to answer the question. The answer is a yes to that question; correct?

A. The dose is dependent upon how much talc gets to the ovaries, yes.

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Q. And you've not done a calculation or experiment to determine what that amount is; correct?
A. That's correct.
Q. All right.
Let me mark Cramer 2016. We discussed it earlier, but we'll mark it for the record. This is a study that you cite in your materials. We'll mark it as Exhibit 26.
(Exhibit No. 26 was marked for identification.)
BY MR. ZELLERS:
Q. You recognize this paper; correct?
A. I've reviewed it.
Q. This is a retrospective case-control study published in 2016; correct?
A. Yes.
Q. You discuss this study in your report on page 9; is that right?
A. Let me turn to page 9.
Q. Sure. I'm looking under "Biologic Gradient/Dose-response" right in the middle.
You claim that (as read):
"A number of studies have demonstrated an association between 'dose' and the occurrence of EOC [or epithelial ovarian

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cancer] (response)."
Is that right?
A. That's correct.
Q. Let's look at what the Cramer study shows.
Turn to page 337 of the Cramer paper, if you will, Exhibit 26 to the deposition.
Do you see Table 1?
A. Yes, sir.
Q. Table 1 shows the risk of ovarian cancer for women who use talc daily for different periods of time -- 1 year, 1 to 5 years, 5 to 20 years, and more than 20 years. Is that right?
A. Yes.
Q. There was only statistical significance for one to five years of use and for more than 20 years of use; is that right?
A. According to the odds ratio and the confidence intervals, yes.
Q. If there is a dose response, shouldn't there continue to be statistical significance with increased exposure?
A. In general, you would think that. But, on the other hand, maybe we don't have to have a dose response to cause cancer.
Q. Well, certainly you've opined in your report

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that there is a dose response; is that right?
A. Yes.
Q. And, in fact, at least looking at Table 1 of the Cramer study, this does not show a dose response; correct?
MS. O'DELL: Object to the form.
THE WITNESS: So, going down that table, there is more of a dose response as we get under the second half of that table, toward "general talc applications."
BY MR. ZELLERS:
Q. There is not a consistent dose response; correct?
A. Not a consistent.
Q. Yes. I mean, you get a statistically significant finding and then a period of time where there's not a statistically significant finding and then another period of time where there is a statistically significant finding; is that right?
MS. O'DELL: Object to the form.
THE WITNESS: As I read through the second half of this table, there's a consistent statistically significant finding beginning after less than 360 applications, equivalent to one year of daily use.

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BY MR. ZELLERS:
Q. Well, when you review, you consider all of the data; correct?
A. Yes.
Q. The top of the Table 1 is not consistent with the bottom of Table 1, at least in terms of statistically significant findings; is that right?
A. The two -- the two vary, depending upon how you quantitate dose.
Q. Another criteria or factor for Bradford Hill is biological plausibility; is that right?
A. Yes.
Q. The biological mechanisms of cancer are not your area of expertise; is that correct?
MS. O'DELL: Object to the form.
THE WITNESS: I think, as a gynecologic oncologist, I have a good understanding of the biological mechanisms of cancer. For example, human papillomavirus causes cervical cancer, vaginal cancer, vulvar cancer, anal cancer, oropharyngeal cancer.
BY MR. ZELLERS:
Q. Do you defer to other experts on the topic of biologic plausibility?
A. I think there are some that know more than I know about it. But I know that, for example, in

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this disease of ovarian cancer caused by talcum powder, inflammation is the most likely cause.
Q. And do you consider yourself to be an expert on the topic of biologic plausibility as it relates to talcum powder and ovarian cancer?
MS. O'DELL: Objection to form. Asked and answered.
THE WITNESS: I think I have a very good understanding of that, and I'm not sure how you define an expert.
BY MR. ZELLERS:
Q. Is all epithelial ovarian cancer caused by the same mechanism?
A. I don't think so.
Q. You stated before that there are different mechanisms; is that right?
A. I said -- yes.
Q. What is the biologic mechanism for serous ovarian cancer?
A. There could be several biological mechanisms for any of the ovarian cancers.
Q. Well, what biologic mechanisms are there, based upon your experience, for serous cancer -- ovarian cancer?
A. One of the biologic mechanisms are BRCA1 to 2

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mutations. And, as I discussed previously, all cancers are caused by mutations of genes that regulate cell growth and result in invasion and metastases.
Q. Any others?
A. Anything else beside gene mutations?
Q. Gene mutations, yes, for serous ovarian cancer.
A. There are always gene mutations causing the cancer. And, therefore, if you're just specifically talking about serous cancers, then gene mutations for all serous cancers occur. They are not normal cells.
Q. Does talcum powder increase all subtypes of ovarian cancer?
MS. O'DELL: Objection. Asked and answered.
THE WITNESS: I think the epidemiologic data would suggest that serous cancers are the most common but endometrioid are there.
And the other study -- other types of epithelial ovarian cancers -- clear cell and mucinous -- are so infrequent -- they're rare cancers. And, therefore, we don't have statistical power to decide whether they're caused by talc or not.
BY MR. ZELLERS:
Q. Different subtypes of epithelial ovarian

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cancer have different biological mechanisms; correct?
A. Again, I'm not sure what you mean by "biological mechanism."
Q. You're not familiar with biological mechanisms that cause ovarian cancer?
A. The biological mechanism that I've been trying to explain to you is gene mutation.
Q. That's the only biological mechanism that causes ovarian cancer, in your experience; is that right?
A. You're talking about what causes ovarian cancer, not the mechanism that becomes ovarian cancer or what ovarian cancer represents.
Q. I'm asking you the mechanism that causes ovarian cancer. And you have told me that, with talcum powder, it is gene mutation; is that right?
MS. O'DELL: Object to the form.
THE WITNESS: As it is for all cancers. As it is for all ovarian cancers.
BY MR. ZELLERS:
Q. If talc is associated with all subtypes of epithelial ovarian cancer or with different subtypes in different studies, doesn't that suggest that the association is by chance?
MS. O'DELL: Object to the form.

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THE WITNESS: So no carcinogen is going to cause cancer in every circumstance in every patient. Some patients may be more susceptible to a carcinogen; others may be more resistant.
Women with BRCA1 mutations don't always develop ovarian cancer, but they are at much higher risk. It usually causes -- it requires a number of mutations before a malignancy occurs, not just one.
BY MR. ZELLERS:
Q. You would agree that different studies have found different associations between talcum powder use and different types of epithelial ovarian cancer; is that right?
A. The -- yes, and because possibly many of those rare cancers, like mucinous cancers and clear cell cancers, are not -- the studies aren't powered to identify those. So we don't know, I guess would be my answer.
Q. Putting aside inhalation for the moment, your opinion is that talcum powder travels from the perineal region to the ovaries through the woman's reproductive tract; is that right?
A. Yes, sir.
Q. So the talcum powder must travel across the vulva, through the labia majora, through the labia

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minora, across the -- and clitoris, across the perineal body, up into the vagina, into the cervical canal, through the cervix and cervical mucosa, or mucus, into the endometrial cavity, through the uterus, into the fallopian tube opening, across the entire length of the fallopian tube to the fimbria, and then into the ovary; is that right?

A. Yes, sir.

Q. If talcum powder can make this migration, can other substances also make the same migration?

A. I presume so.

Q. Sand from the beach?

A. I think the particle size may have some bearing on how far it can get up the reproductive tract.

Q. Toilet paper particles?

MS. O'DELL: Object to the form.

THE WITNESS: Again, depends upon the particle size.

BY MR. ZELLERS:

Q. There is no human study that demonstrates the migration of any particulate matter from the perineum to the ovaries; correct?

MS. O'DELL: Object to the form.

THE WITNESS: Number of studies that

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show that once it's in the vagina, it can migrate --

BY MR. ZELLERS:

Q. There is --

A. -- to the ovary.

Q. But the answer to my question is correct. There are no human studies that demonstrate the migration of any particulate matter from the perineum to the ovaries; correct?

MS. O'DELL: Object to the form.

THE WITNESS: Nobody has studied it that I'm aware of.

BY MR. ZELLERS:

Q. None of the articles you cite in your report actually looked at whether talc can migrate from perineal application through the fallopian tubes to the ovaries; correct?

MS. O'DELL: Object to the form.

THE WITNESS: Well, if you go to Langseth, for example, on the second page underneath the forest plot at the end of the second full paragraph -- I'm sorry. I've got your exhibit.

BY MR. ZELLERS:

Q. Well, you have the exhibit. I should have a copy.

A. Okay.

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Q. And my question to you is --

MS. O'DELL: I think he was finished -- he wasn't finished.

THE WITNESS: I was going to read this to you from Langseth. And the sentence says (as read):

"The evidence of talc migrating to the ovaries lends credibility to such a possible association."

BY MR. ZELLERS:

Q. Can you answer my question?

A. I was reporting to you a study.

Q. I need you to answer my question if you can.

A. Okay.

Q. I'll ask it again.

Is there any human study that demonstrates the migration of any particulate -- and let me withdraw that, because I think I moved on to the next question.

None of the articles that you cite actually looked at whether talc can migrate from the perineal application through the fallopian tubes to the ovaries; correct?

MS. O'DELL: Object to the form.

THE WITNESS: That's correct.

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BY MR. ZELLERS:

Q. All right. You also cannot cite any article that shows granulomas, fibrosis, or adhesions anywhere up the reproductive tract of a woman as a result of her external genital talc application, can you?

MS. O'DELL: Object to the form.

THE WITNESS: No.

BY MR. ZELLERS:

Q. Let's talk about the studies that you cite in your report in support of your theory of migration.

MS. O'DELL: Object to -- excuse me. Sorry.

MR. ZELLERS: It's okay.

MS. O'DELL: I apologize.

BY MR. ZELLERS:

Q. In support of your theory of migration, you discuss sperm. I'm looking at page 7, last paragraph that carries over onto page 8. Is that right?

A. I have it.

MS. O'DELL: Object to form.

BY MR. ZELLERS:

Q. Sperm have tails and motility; is that right?

A. Yes, and that's acknowledged in my report.

Q. Sperm affirmatively move themselves up the reproductive tract; is that right?

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A. They can.
Q. You cite Egli, 1961, the carbon particle study. Are you familiar with that, or do you need me to hand you another copy?
A. I've reviewed it before. It's been a little while.
Q. Well, let me ask you a couple of questions.
A. Sure.
Q. And if you need the study, then I'll be happy to have you take a look at it.
Egli did not involve talcum powder; correct?
A. No. These are carbon particles.
Q. Egli used carbon particles that were suspended in a solution that had the consistency of seminal fluid; is that right?
MS. O'DELL: If you need to take a moment to review, Doctor, feel free to do that.
THE WITNESS: They were suspended in dextran suspension.
BY MR. ZELLERS:
Q. Is that seminal fluid, fluid that sperm are suspended in?
A. No.
Q. What solution were they suspended in?
A. Dextran.

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Q. What support do you have for the proposition that talcum powder behaves similarly to carbon particles suspended in a dextran fluid-like substance?
A. I think it's very similar to talcum powder particles progressing up. Dextran is a thick, glucose-rich medium that is much like vaginal fluid, if you will.
Q. It's a fluid; right?
A. Yes.
Q. Talcum powder is a particle; correct?
A. Once talcum powder gets into the vagina, it becomes part of the vaginal fluid.
Q. The Egli study involved three women; is that right?
A. Yes.
Q. Tiny sample size; correct?
A. Yes.
Q. They used intramuscular oxytocin to aid the transport of the particles; is that right?
A. Yes. It stimulated the uterus to contract.
Q. And for the administration of the carbon particles, the women were laying on their backs with their heads tilted at a downward angle; is that right?
A. That's what it says.
Q. Do you agree that laying down with their

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heads tilted downward is a very -- is very different from the way in which women generally apply talcum powder to their perineal region?
A. Honestly, I don't know how they apply talcum powder to their perineal region. I would imagine they're not with their head down, but they may be sitting, they may be standing, they may be lying.
Q. Based upon your experience, it's different; correct?
A. I don't have any experience with talcum powder application.
Q. Right. So you don't know whether or not most women apply talcum powder to their perineal region with their head toward the ground and their legs up in the air?
MS. O'DELL: Object to the form.
THE WITNESS: I think it's unlikely that they have their heads to the ground and legs in the air, but they have probably multiple positions they could apply it in.
BY MR. ZELLERS:
Q. Even with these artificial conditions, the researchers only found carbon particles in the fallopian tubes of two of the three women; is that right?

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A. I think that's what the results said.
Q. Are you familiar with the Venter 1979 study that you cite?
A. I'll have to pull it back out to refresh my memory. It's been a few months since I looked at that.
Q. Well, can I ask you a few questions about it?
A. If I can answer them, I will. Sure.
Q. Is this the radioactive marker study?
A. Yes.
Q. That study did not involve talcum powder; it involved a particle with a radioactive tracer. Is that right?
A. Yes. Technetium albumin in microspheres.
Q. What support do you have for the proposition that talcum powder behaves similarly to this kind of particle?
A. I think that talcum powder is similar to these particles. It's small and can migrate.
Q. In the study it involved a small sample size; right? Only 24 women?
MS. O'DELL: Object to the form.
THE WITNESS: Yes.
BY MR. ZELLERS:
Q. The women laid on their backs with their

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buttocks elevated; is that right?
A. When it was applied, and then the patients didn't undergo surgery until the next day. So the patients, after being in the position where the talc -- where the radioactive tracer was applied, were then up and about until they came in for surgery the next day. So they were in different positions.
Q. Is that really what you think, based upon your review of the study?
A. You don't think that the patient was laying in bed for 24 hours until she had surgery?
Q. Doctor, your recollection of this study is that the radioactive tracer marker was used and then the women were up and around?
MS. O'DELL: Object to the form.
BY MR. ZELLERS:
Q. In fact, after the radioactive marker was administered, the women remained laying in the position with their -- on their backs with their buttocks elevated for two hours, with their legs pressed together; is that right?
A. I would have to find it to refresh my memory.
Q. If that's true, that would be different than your understanding of how women use talcum powder in the genital area; correct?

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MS. O'DELL: Objection. Misstates the doctor's testimony.
If you need to review --
THE WITNESS: Again, I don't think that we know -- I know how women apply talcum powder. But these women didn't lay supine for 24 hours until they had their surgery, when they found the radioactive microspheres in the ovary.
BY MR. ZELLERS:
Q. Do you know whether or not they laid supine for two hours after the radioactive marker was administered with their legs pressed together?
A. Yes.
Q. Yes, you agree with that; correct?
A. Yes.
Q. And even under these artificial conditions, the researchers only found radioactive activity in the fallopian tubes or ovaries of 9 of the 21 women; is that right?
MS. O'DELL: Object to the form.
THE WITNESS: That's what they reported in 24 hours.
BY MR. ZELLERS:
Q. You cite Sjosten, 2004, the glove study; is that right?

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A. I did.
Q. That study did not involve talcum powder; it involved starch. Is that right?
A. Yes.
Q. Sjosten involved the researchers examining the women's cervix with their fingers; is that right?
Are you able to answer that question?
A. I need to read along with you.
So they examined -- they did a pelvic exam, a bimanual exam on the patients.
Q. Examining the women's cervix with their fingers; is that correct?
A. And examining the vagina.
Q. What is your basis for saying that pressing gloved fingers against the cervix is comparable to an external dusting of talcum powder?
MS. O'DELL: Object to form.
THE WITNESS: I think it deposits the substance, the powder, against the cervix.
BY MR. ZELLERS:
Q. And the study found particles in the reproductive tract of women who were examined with powder-free gloves; is that right?
A. I believe so.
Q. You cite the Heller study of women's ovaries

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after surgical oophorectomy; is that right?
A. Yes.
Q. Didn't Heller find talc in tissues of all 24 patients, including the 12 who did not use perineal talc?
A. Give me a moment.
Q. Let me try to ask it this way so that we can move on.
Do you have any reason to dispute that Heller found talc in tissues of all 24 patients, including the 12 who did not use perineal talc?
MS. O'DELL: Object to the form.
THE WITNESS: Yes, as long as there's not an issue with recall bias.
BY MR. ZELLERS:
Q. If talcum powder migrates from the perineal region to the ovaries, shouldn't exposure to talc be far greater in concentration in the rectal, vulvar, vaginal, cervical, and uterine tissues which are closer to the area of initial exposure?
MS. O'DELL: Object to the form.
THE WITNESS: I'm not sure what the basis of that observation is. The urethra and anus have sphincters. The urethra and anus also have an exit mechanism by urination or defecation.

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BY MR. ZELLERS:
Q. So you -- I just want to make sure I'm clear. You disagree that -- if talcum powder migrates from the perineal region to the ovaries, you disagree that exposure to talc would be greater in concentration in the rectal, vulvar, vaginal, cervical, and uterine tissues; correct?
MS. O'DELL: Objection. Asked and answered.
THE WITNESS: I'm not understanding your question. Would be greater where?
BY MR. ZELLERS:
Q. Would be greater in the rectal, vulvar, vaginal, cervical, and uterine tissues than in the ovaries.
MS. O'DELL: Objection. Asked and answered.
THE WITNESS: I don't have any evidence about the rectum or the urethra. And it would be -- yes, more likely than not, there would be more on the vulva than on the ovaries. All of it that goes on the vulva does not land on the ovaries.
BY MR. ZELLERS:
Q. Talc particles should be causing inflammation in all those organs and areas if your theory is

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correct; is that right?
A. No.
MS. O'DELL: Object to the form.
BY MR. ZELLERS:
Q. Why would you not expect inflammation in the rectal, vulvar, vaginal, cervical, and uterine tissues?
MS. O'DELL: Object to the form.
THE WITNESS: So there's no -- no evidence that this talc gets into the rectum that I'm aware of, unless you have some evidence that I'm not seeing.
BY MR. ZELLERS:
Q. Why do talc particles not cause inflammation in the other organs and areas?
A. I think the other organs -- the vagina, cervix, uterus, and fallopian tubes -- are different tissues; and different tissues have different susceptibility, if you will, to the impact of talcum powder and its contents.
Q. What is it about the tissues of the vulvar, vaginal, cervical, and uterine areas that would result in talc not causing inflammation to those tissues but causing, at least under your theory, inflammation to the ovary?

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MS. O'DELL: Object to the form.
THE WITNESS: Because the ovary has a different epithelium, a different surface. The vagina -- I'm sorry -- the vulva, vagina, and exocervix are all squamous epithelium. They are much more susceptible to HPV. So I can turn around the explanation and say HPV doesn't infect the endometrium -- the uterus, fallopian tubes, or ovaries. So some tissues are more susceptible to a carcinogen than others.
BY MR. ZELLERS:
Q. What study are you referring to for that proposition?
A. About HPV?
Q. No. About the tissue being the same -- strike that.
Tissue being different and not susceptible to inflammation from talc in the human vulvar, vaginal, cervical, and uterine tissues.
MS. O'DELL: Object to the form.
THE WITNESS: They are all different tissues, and we have not seen any inflammation or cancer associated with talcum powder in those organs.
BY MR. ZELLERS:
Q. Is there a study that you're referring to

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that finds that there is not inflammation from talc to those tissues?
MS. O'DELL: Object to the form.
THE WITNESS: I don't have a study, but, obviously, it's not associated with cancers of those tissues.
BY MR. ZELLERS:
Q. There are no studies that show inflammation as a result of genital talc use result in cancer in those areas; is that right?
MS. O'DELL: Objection to form.
THE WITNESS: In what areas now are you talking about?
BY MR. ZELLERS:
Q. Let me make it even simpler.
There's no studies that show inflammation as a result of genital talc use in the vulvar, vaginal, cervical, and uterine areas; is that right?
A. That's correct.
MS. O'DELL: Object to the form.
BY MR. ZELLERS:
Q. There are no studies that show a link between external genital talc use and rectal, vulvar, vaginal, cervical, or uterine cancer; is that right?
A. That's correct.

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Q. In Exhibit B of your report, you include a study published by Huncharek in 2007. That's page 11. Do you recall that study?
A. No, but I'd like to refresh my memory.
MS. O'DELL: Which Huncharek?
MR. ZELLERS: 2007.
BY MR. ZELLERS:
Q. Do you have that easily available? This is a study that you cite in your materials reviewed; is that right?
A. Yes.
Q. It's a meta-analysis of studies and the relationship between ovarian cancer and using diaphragms that are dusted with talcum powder; is that right?
A. Yes.
Q. A diaphragm is inserted directly onto a woman's cervix; is that right?
A. Yes.
Q. You did not include Huncharek 2007 in your list of meta-analyses regarding talc and ovarian cancer on page 7 of your report, did you?
MS. O'DELL: Object to the form.
THE WITNESS: No, because it wasn't dealing with applying talcum powder to the vulva,

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perineum.
BY MR. ZELLERS:
Q. Well, your theory, putting aside inhalation, is that the talcum powder travels from the perineal region through the vagina through the cervix through the uterus and then into the fallopian tubes; is that right?
A. Yes.
Q. How, then, do you validate excluding data about the relationship between ovarian cancer and talcum powder that is applied directly to the cervix?
MS. O'DELL: Object to the form.
THE WITNESS: Because it's not the volume of talcum powder that is used on the vulva. And, over a period of time, application of diaphragms is most likely much less likely than somebody using talcum powder on the vulva on a daily basis.
BY MR. ZELLERS:
Q. On what study are you relying for that statement?
A. My clinical experience of understanding the sexual lives of women. They don't use diaphragms every day, in most cases.
Q. Are you aware of any study that talcum powder affects the body differently when it is applied to the

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perineal region and travels to the cervix compared to when it is applied directly to the cervix?
MS. O'DELL: Object to the form.
THE WITNESS: I'm not aware of any study, no.
BY MR. ZELLERS:
Q. When applied to the perineal region, the talcum powder would also be in close contact with a woman's urethra; correct?
A. Yes.
Q. Substances are capable of traveling up the urethra; right?
A. Not that I know of, except for bacteria.
Q. Women get urinary tract infections when bacteria travels up the urethra; right?
A. I recognize that as a modal -- motile, like sperm and bacteria, when I discuss lower genital tract migration from the vagina up into the tubes and ovaries with sperm and sexually transmitted infection. So, yes, women get urinary tract infections.
Q. Studies do not show an increase in bladder cancer with talcum powder use; is that right?
A. That's right. The bladder is a different epithelium than the ovary.
Q. And studies do not show an increase in rectal

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cancer with talcum powder use; is that right?
A. That's correct.
MS. O'DELL: Objection. Asked and answered.
BY MR. ZELLERS:
Q. Are you opining on inhalation exposure as a plausible mechanism for talcum powder to reach the ovaries, or do you defer to other experts on that?
A. I think there's literature that suggests that it's a lower possibility, but inhalation of asbestos can increase the risk of ovarian cancer.
Q. Well, you rely in part on Steiling 2018; is that right? This is at page 8 of your report.
A. IARC and the Steiling.
Q. Right. Steiling 2018 deals generally with cosmetic powders, not talcum powder; correct?
A. I need to look at the paper again.
Q. Well, either your counsel can hand it to you or I can hand it to you.
MR. ZELLERS: Did you find it, Counsel?
BY MR. ZELLERS:
Q. Do you have the Steiling paper in front of you?
A. Yes --
MS. O'DELL: Do you have a copy for me,

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please, if you don't mind. Thank you.
Are you going to mark that, Mike, or are you --
MR. ZELLERS: If you want me to mark it, I can. I think we all know what it is.
MS. O'DELL: I'm just asking.
MR. ZELLERS: Would you like it marked?
MS. O'DELL: Only if you were going to mark it, I was just going to put a number on it.
MR. ZELLERS: Well, I just have a few basic questions.
BY MR. ZELLERS:
Q. So, Doctor, my first question is the Steiling 2018 deals generally with cosmetic powders, not talcum powder specifically; is that right?
A. Apparently so, yes.
Q. And Steiling 2018 just discusses the fact that particles can be inhaled; is that right?
A. Yes.
MS. O'DELL: Object to the form.
BY MR. ZELLERS:
Q. It says nothing about inhaled particles migrating to the ovaries, does it?
A. No.
Q. In fact, it says nothing about inhaled

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particles migrating anywhere, does it?
MS. O'DELL: Objection.
THE WITNESS: It doesn't talk about migration. You're right.
BY MR. ZELLERS:
Q. And it also says nothing about inhaled particles causing ovarian cancer; is that right?
A. In this particular study, although we know from asbestos studies that it does.
Q. Well, don't studies of talcum powder use fail to show statistically significant association between nongenital use of talcum powder and ovarian cancer?
A. I believe so.
Q. If inhaled talc could migrate to the ovaries, wouldn't you expect to see increased ovarian cancer risk with nongenital use of talcum powder?
MS. O'DELL: Object to the form.
THE WITNESS: In other words, inhaled. I think the inhalation is much smaller, but, to date, we haven't seen an increased risk of ovarian cancer.
BY MR. ZELLERS:
Q. With inhaled talcum powder; correct?
A. With inhaled talcum powder.
Q. And that was a finding that you read about in Cramer 2016 as well as other places; correct?

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MS. O'DELL: Object to the form.
BY MR. ZELLERS:
Q. I'll withdraw the question and move on.
Do you agree -- well, strike that.
You assert that talcum powder, when it reaches the ovaries, it elicits an inflammatory response that is linked to ovarian cancer; is that right?
A. Yes. I think that's the mechanism by which gene mutation occurs.
Q. Is it your opinion -- strike that.
Is your opinion related to all of the different histologic types of epithelial ovarian cancer?
MS. O'DELL: Objection. Asked and answered.
THE WITNESS: I think an inflammatory response happens on the ovarian epithelium, and some ovarian cancers -- some epithelial ovarian cancers are more common, serous carcinoma being the most common.
BY MR. ZELLERS:
Q. Is it your opinion that inflammation is a cause of clear cell and mucinous ovarian cancer? Or do you not have an opinion?
A. I don't have an opinion.

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Q. You have not done an expert review of the inflammation evidence yourself, have you?
MS. O'DELL: Object to the form.
THE WITNESS: I'm aware of -- I've done a review and have been aware of inflammation in gynecologic cancers, especially ovarian cancer, with elevated serum biomarkers suggesting inflammation and also more biologic -- the laboratory work that Dr. Saed and others have done.
BY MR. ZELLERS:
Q. You do know that not all inflammatory conditions lead to cancer; correct?
A. Yes.
Q. There's conditions that are inflammatory reactions that all of us may have -- or that folks may have that don't lead to cancer, such as rheumatoid arthritis; is that right?
A. That's, best as I understand, rheumatoid arthritis.
Q. Same with psoriasis; is that right?
A. Yes.
Q. Those are chronic inflammatory diseases; correct?
A. Of the skin.
Q. Rheumatoid arthritis is a chronic

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inflammatory disease of the skin?
A. It can have -- in joints. There can be a skin component to rheumatoid arthritis. I thought you were talking about psoriasis.
Q. How does an acute inflammatory response lead to cancer?
A. An acute inflammatory response, I don't believe, leads to cancer.
Q. You have -- well, strike that.
On page 9 of your report, you conclude that (as read):
"Talcum powder products is a causative factor in the development of epithelial ovarian cancer."
Is that right?
A. Yes.
Q. We can change that now based upon your testimony that talcum powder products is a causative factor in the development of serous ovarian cancer; correct?
MS. O'DELL: Object to the form.
THE WITNESS: I think I would stay with epithelial ovarian cancer till we have more data.

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BY MR. ZELLERS:
Q. How do you define the term "talcum powder products"?
A. Talcum powder products are Johnson's baby powder and Shower to Shower.
Q. Are other consumer talcum powder products included in your conclusions?
A. Yes, but Johnson & Johnson has the market share, as I understand it.
Q. Do you understand that some of the talc epidemiology separates use by type of talcum powder product?
MS. O'DELL: Object to the form.
THE WITNESS: I'm not sure what you mean by type of talcum powder.
BY MR. ZELLERS:
Q. Do you include talc-containing deodorizing sprays in your definition of talcum powder products?
THE WITNESS: No. We've been talking today, I thought, about Johnson -- as you defined it to start the day as Johnson & Johnson baby powder and Shower to Shower.
BY MR. ZELLERS:
Q. Is there a certain amount of talcum powder that a product must contain to cause inflammation?

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A. We don't know that information.
Q. Do you consider cornstarch to be a talcum powder product that causes inflammation?
MS. O'DELL: Object to the form.
THE WITNESS: It's not a talcum powder product.
BY MR. ZELLERS:
Q. What about a product like Shower to Shower, which contains cornstarch and talcum powder?
A. And your question is?
Q. My question is, is there a certain amount of talcum powder that a product must contain to cause inflammation?
A. Not that we're aware of.
Q. 1 percent talcum powder, 99 percent cornstarch, that could cause inflammation resulting in epithelial ovarian cancer. Is that your testimony?
A. I think that's possible.
Q. What methodology have you arrived -- strike that.
What methodology have you employed to arrive at the conclusion that the Shower to Shower product causes inflammation?
A. It has talcum powder in it.
Q. Your opinion that talcum powder products

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cause inflammation is not based on the determination that there is a threshold amount of talcum powder that is required to be in the product before you can conclude that the product will cause chronic inflammation; correct?
MS. O'DELL: Object to the form.
THE WITNESS: I think there's no threshold amount that -- below which the patient that's exposed to talcum powder is safe.
BY MR. ZELLERS:
Q. Is there a study that you can cite me to for that proposition?
A. No, except that, overall, women that have been exposed to talcum powder in the perineum have an increased risk of ovarian cancer. And we don't know the quantity in each individual patient. So some patients may have had a small amount and developed ovarian cancer, unfortunately.
Q. If inflammation is the issue, why would cornstarch be a superior alternative to talc?
A. Because I don't believe cornstarch causes chronic inflammation. It's absorbed by the body. Macrophages come in and clear it out. It's not a permanent mineral like talc is.
Q. Are you aware that the FDA banned the use of

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cornstarch on surgical gloves because of the risk of inflammation, granulomas, fibrosis, adhesions, and irritation?

A. Yes, because that was causing an acute inflammation, not a chronic inflammation.

Q. Are you aware, though, that that was the reason the FDA banned the use of cornstarch on surgical gloves?

A. They were trying to stop adhesion formation after surgery.

Q. So you are aware of that; is that right?

A. Yes. When I was coming up, we had to wash our gloves before we operated, for that reason.

Q. How many patients with ovarian cancer have you operated on over the course of your career?

A. I would say probably 30 women a year over 40 years.

Q. For those patients that had nonendometrioid ovarian cancer, have you seen evidence of inflammation when you operated?

MS. O'DELL: Object to the form.

THE WITNESS: When I operated, 75 percent of these patients have cancer all over their abdominal and peritoneal cavity, and identifying inflammation visually from the cancer is something a

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surgeon or any doctor can't do.

If you look at histologic specimens of the tumor -- the cancer, we see inflammation, we see lymphocytes and other inflammatory cells. And, in addition, you see inflammatory biomarkers like CA-125.

BY MR. ZELLERS:

Q. At least grossly, when you operate on patients with nonendometrioid ovarian cancer, you do not see evidence of inflammation; correct?

MS. O'DELL: Object to the form.

THE WITNESS: Well, I see --

MS. O'DELL: I'm sorry.

THE WITNESS: -- probably more acute inflammation. We do see additional increased peritoneal fluid, what's called ascites, which is probably an inflammatory response to the cancer.

BY MR. ZELLERS:

Q. Do you see adhesions?

A. Sometimes.

Q. So it's your testimony that, when you operate on patients with nonendometrioid ovarian cancer, you do see evidence of inflammation grossly; is that right?

A. Yes, with ascites.

Q. What else?

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A. That's about the only thing that I can determine with my naked eye as to what looks like inflammation.

Q. You see that in some patients but not all patients with ovarian cancer; correct?

A. That's true. That's not the only thing that is related to inflammation.

Q. For your patients with a nonendometrioid ovarian cancer, has microscopic examination of their tissues shown evidence of activation of an inflammatory cascade?

MS. O'DELL: Object to the form.

THE WITNESS: I don't think that pathologists look at that. And I'm not sure exactly what you would identify histologically in an inflammatory cascade. I described to you lymphocytes, for example, that represent inflammation.

BY MR. ZELLERS:

Q. Has it shown evidence of granulomas?

A. No.

MS. O'DELL: Object to the form.

BY MR. ZELLERS:

Q. Has it shown evidence of foreign body or giant cell reactions?

A. Not that I'm aware of.

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Q. Do you believe that every time a talc particle enters the human body, it produces an inflammatory response?

A. A talc particle? Are we talking about platy talc or fibrous talc or what kind of talc --

Q. Talcum powder. Do you believe that every time a talc particle -- talcum powder enters the human body, it produces an inflammatory response?

A. I think it does on a microscopic basis, yes.

Q. You rely on Heller 1996 for the idea that talc can migrate to the ovaries. We talked about the Heller paper; right?

A. Yes.

Q. And, in fact, didn't Heller find that there was no reaction in the ovaries to the talc particles?

A. I'd like to look at that paper again --

Q. Sure. Take --

A. -- because we were talking along the lines of what ovarian cancer patients look like and now we're back to --

Q. I can get it for you or your counsel can show you.

I'm looking at Heller 1996, page 1508, right column, second-to-last paragraph.

Counsel, is it easier for me to find it?

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MS. O'DELL: Yeah, why don't you do that?
MR. ZELLERS: All right. We'll mark the Heller paper that we discussed previously as Exhibit 27.
(Exhibit No. 27 was marked for identification.)
BY MR. ZELLERS:
Q. Doctor, is this the paper we talked about previously and that you reviewed and are relying on in this case?
A. Yes.
Q. Turn, if you will, to page 1508, the second page. And I'm looking on the right-hand column just two sentences above "Comment" (as read):
"There was no evidence of response to talc, such as foreign body giant cell reactions or fibrosis in the tissue."
Did I read that correctly?
A. Yes.
Q. What evidence is there that externally applied talcum powder causes chronic inflammation?
A. Again, I think we see increased biomarkers. I think Dr. Saed's research using ovarian cancer cells shows the inflammatory response that results in gene

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mutations.
Q. Well, we talked a bit ago, you're unaware of any reports or studies in the literature of externally applied talc leading to inflammation, granulomas, fibrosis, or adhesions anywhere along a woman's reproductive tract; is that right?
MS. O'DELL: Object to the form.
THE WITNESS: So what you're describing with adhesions is a reaction -- is an acute reaction -- acute inflammatory reaction, not a chronic reaction.
BY MR. ZELLERS:
Q. My question is if up to 50 percent of US women have used genital talc, shouldn't this be a common finding, inflammation, granulomas, fibrosis along a woman's reproductive tract?
MS. O'DELL: Object to the form.
THE WITNESS: Those conditions you're describing are the reaction to an acute inflammation. We're talking about chronic inflammation.
BY MR. ZELLERS:
Q. So your testimony is inflammation, granulomas, fibrosis, or adhesions are inconsistent with and not associated with chronic inflammation in your experience; is that right?

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MS. O'DELL: Object to the form.
THE WITNESS: That's correct.
BY MR. ZELLERS:
Q. In your report, you state (as read):
"An inflammatory reaction caused by talcum powder on the tube and surface of the ovary results in genetic mutations and carcinogenesis."
Is that right?
A. Yes.
Q. And you cite on page 9 in your report -- well, strike that.
So what authority supports that statement?
A. What was the question again?
Q. Sure. In your report, page 9, under "Plausibility," second sentence, you state (as read):
"An inflammatory reaction caused by talcum powder on the tube and surface of the ovary results in genetic mutations and carcinogenesis."
What authority supports that statement?
A. The sequence of events from perineal talc exposure to ovarian cancer and the mechanism of

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chronic inflammation on that ovary over a period of time results in the gene mutation which then becomes ovarian cancer.
Q. On what authority, on what study, are you relying for that statement?
A. On the epidemiologic data showing that the use of perineal talc results in ovarian cancer.
Q. But those studies don't state and find that it's an inflammatory reaction caused by talcum powder on the tube and the ovary, do they?
A. By the time the patient has ovarian cancer, you don't see that.
Q. So my question is you've made the statement, "An inflammatory reaction caused by talcum powder on the tube and surface of the ovary results in genetic mutations and carcinogenesis."
What study can I go look at, what study can I read, what study are you relying on for that statement?
A. What I just described to you. The study is that the patients have ovarian cancer.
Q. Please name the study that you're relying on for that proposition.
A. All the epidemiologic studies that we've been talking about today in totality show the association

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between the exposure of talcum powder to women's perineum and ovarian cancer.
Q. And it's your testimony that all of those studies discuss the inflammatory reaction as the causal mechanism; is that right?
MS. O'DELL: Object to the form.
THE WITNESS: Those studies do not discuss the mechanism in all studies. Some do.
BY MR. ZELLERS:
Q. So here's what I want: You're saying here "An inflammatory reaction caused by talcum powder on the tube and surface of the ovary results in genetic mutations and carcinogenesis."
What study are you referring to, are you relying on, for that statement?
A. That the patient got ovarian cancer. She had carcinogenesis. She had gene mutations caused by chronic inflammation that led to cancer. And then we operated on the patient and found she had cancer.
Q. What is the study that says that the mechanism, the biologic mechanism, was an inflammatory reaction caused by talcum powder on the tube and surface of the ovary?
A. Would you like to turn to laboratory studies?
Q. Is there a study that you're relying on for

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that statement?
A. There's no way somebody could do a study.
Q. All right.
A. They do serial biopsies of the ovary, watch for those gene mutations, and then watch for cancer to occur, and then say, hey, chronic inflammation led to cancer several years later. I don't know how anybody could do such a study.
Q. In your report, you state -- this is also on page 9, under "Coherence" (as read):
"Epidemiologic data, in vitro and in vivo research, are consistent in explaining the pathogenesis of epithelial ovarian cancer through the inflammatory methods described above."
Did I read that correctly?
A. Yes, sir.
Q. How does epidemiological data support your inflammation theory?
MS. O'DELL: Objection to the form.
THE WITNESS: The inflammation theory is the only plausible theory that I think we have to explain why talcum powder can cause ovarian cancer.
And we see, then, in Dr. Saed's laboratory

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that inflammation is occurring when Johnson's baby powder is put into culture with a very normal ovarian cancer -- normal ovarian cells.
BY MR. ZELLERS:
Q. You'd agree that the research regarding whether chronic inflammation can cause ovarian cancer is ongoing; is that right?
A. I think cancer research in general is ongoing.
Q. Most of the studies that you cite talking about chronic inflammation refer to chronic inflammation as a hypothesis of one of the ways cancer might form in the ovary; is that right?
MS. O'DELL: Object to the form.
THE WITNESS: I think it's the most likely -- more likely than not that's the reason that ovarian cancer forms on the ovary.
BY MR. ZELLERS:
Q. But it is a hypothesis which scientists and medical professionals are studying; is that right?
MS. O'DELL: Objection to form.
THE WITNESS: It's being studied, and evidence coming out of laboratories is confirming that hypothesis that we have in human beings.

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BY MR. ZELLERS:
Q. You are familiar with a paper published by Merritt in 2008, "Talcum Powder, Chronic Pelvic Inflammation, and NSAIDs in Relation to Risk of Epithelial Ovarian Cancer"; is that right?
A. I've seen it.
Q. All right. And you cite that in Exhibit B to your report. We've marked that as Exhibit 6 to this deposition.
That's an Australian-wide case-control study of around 1500 women with invasive and low malignant potential ovarian tumors and 1500 population-based controls.
Does that refresh your recollection?
MS. O'DELL: Are you speak of Merritt 2007?
MR. ZELLERS: I thought I was speaking of Merritt 2008, which the doctor refers to in his additional materials-considered list on page 17.
MS. O'DELL: Let's make sure we've got that. And that's "Talcum Powder, Chronic Inflammation, NSAIDs in Relation to the Risk of Epithelial Ovarian Cancer"?
MR. ZELLERS: That's correct.
MS. O'DELL: Okay.

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BY MR. ZELLERS:
Q. And let me try to cut to the chase, Doctor, so when you look at it, we can --
The study concludes that, on balance, chronic inflammation does not play a major role in the development of ovarian cancer; is that right?
A. I would have to reread this study if you're reading from some particular place. I don't recall exactly how this study was even designed or executed.
Q. Take a look -- and we'll mark this as an exhibit. Deposition Exhibit 28 is the Merritt paper.
(Exhibit No. 28 was marked for identification.)
BY MR. ZELLERS:
Q. Doctor, is this the same as what you're looking at there?
A. Yes.
Q. This is a study that you cite in support of your opinions; is that right?
MS. O'DELL: Object to the form. I think it's referenced in his materials list. It's not cited in his report.
BY MR. ZELLERS:
Q. It's a study that you felt was at least important enough to refer to in your materials-considered list; is that right?

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A. Along with all these other materials, yes.
Q. Well, if we go to the "Discussion" on page 174 of Deposition Exhibit 28 -- are you with me on 174?
A. I'm on 174. Which paragraph?
Q. Well, the very first --
A. Can I back up? I'd like to refresh my memory of what this study was about.
It was a case-control study, 1500 patients. Confirmed statistical significance of increased ovarian cancer risk associated with use of talc. Relative risk 1.17. Strongest were serous. I'm trying to get down to your inflammation question.
Q. Well, it also talks about --
MS. O'DELL: I don't think the doctor was finished.
MR. ZELLERS: Okay. If the doctor wasn't finished, what else do you need to say, Doctor, before --
THE WITNESS: I'm trying to find out where -- all's I'm reading is the abstract, not even the details of the study so far.
BY MR. ZELLERS:
Q. So I'd like you to go to "Discussion," which is on page 174.

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A. Okay. Without knowing what -- how we got to this discussion, go right ahead.
Q. Well, I'm citing your paper or at least one of the papers you read and considered.
A. I have not read every word of every one of these papers. And you can imagine that, and you can appreciate that.
Q. You've not read the studies that are contained in your materials-considered list --
MS. O'DELL: Objection.
BY MR. ZELLERS:
Q. -- Exhibit 6 to the deposition?
MS. O'DELL: Excuse me. Objection. Misrepresents his testimony.
What's your question?
BY MR. ZELLERS:
Q. Well, do you want to answer that question? You've not read each and every one of the studies; correct?
MS. O'DELL: Objection. Misrepresents his testimony. I think what he had testified to earlier is that he had not read every word of every study but had read the abstracts of -- certainly of every one.
THE WITNESS: Right. And I haven't

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committed every abstract to memory. I'm sure you can appreciate that too.
BY MR. ZELLERS:
Q. I can, and that's why you have it in front of you.
A. Okay.
Q. So if we go to page 174, "Discussion," do you see that? See that paragraph on the left-hand side?
A. I see the page. Which paragraph do you want to see?
Q. Well, do you see the word "Discussion"?
A. Yes.
Q. All right. The first paragraph under "Discussion," the last sentence (as read):
"These results, in combination with previous studies, suggest that chronic inflammation is unlikely to play a major role in the development of ovarian cancer."
Is that the statement -- did I read that correctly?
A. I don't think so. Says (as read):
"May be linked to increased risk of developing ovarian cancer."

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Are we reading the same -- you're reading the first sentence under "Discussion"?
Q. No. I'm reading the last sentence of "Discussion" -- last sentence of the first paragraph.
A. Okay. You read it correctly.
Q. All right. And then if we go to the right-hand side, on the same page of the last paragraph, the first two sentences state (as read):
"If inflammation plays a role in the etiology of ovarian cancer, then it would be expected that PID would be associated with increased risk of ovarian cancer. PID was not associated with elevated risk of ovarian tumors in our data, confirming several previous reports of no association with PID in studies of all subtypes of ovarian cancer."
Did I read that correctly?
A. You did.
Q. So this study concludes that, on balance, chronic inflammation does not play a major role in the development of ovarian cancer; correct?
A. So PID is pelvic inflammatory disease. Is

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that what you understand it?
Q. Yes.
A. So pelvic inflammatory disease is an acute infection treated with antibiotics and usually resolves with proper treatment. So it's not a chronic infection. Having said that, PID is recognized as a risk factor in many of the studies -- many of the documents that you've referred to earlier this morning.
So this particular case-control study doesn't identify PID as a risk; but, in totality, pelvic inflammatory disease is considered a risk factor for ovarian cancer.
Q. What study do you rely on for your opinion that pelvic inflammatory disease is a risk factor or causative of ovarian cancer?
A. If I could turn back to the documents you were using earlier today from either the CDC or --
Q. And just refer to them generally, and then we'll take a look. The CDC --
A. Well, I mean, the risk -- I'm not sure which one it was, but they are --
Q. Let me ask another question, then.
What methodology did you employ to consider the findings of the Merritt paper in coming to the

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opinions contained in your report?
MS. O'DELL: Objection to form.
THE WITNESS: That it is well established, in my opinion, that pelvic inflammatory disease is a risk factor for ovarian cancer.
BY MR. ZELLERS:
Q. Do you agree you cannot ignore the data that doesn't support your opinion and are only relying or looking at data that does support your opinion?
MS. O'DELL: Object to the form.
THE WITNESS: My opinion is based on a larger body of evidence and that other authorities, not my opinion, have established that PID is a risk factor.
MS. BOCKUS: Object. Nonresponsive.
MR. ZELLERS: Move to strike as nonresponsive.
BY MR. ZELLERS:
Q. Do you agree that in doing a proper expert analysis, you need to review and consider the studies that both support your opinions and the studies that do not support your opinions?
A. Absolutely. That's my methodology.
Q. And you believe that you have done that in the discussion in your report; is that right?

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A. I believe so.
Q. All right. Do you agree that the studies relating to NSAIDs are not consistent in terms of establishing that NSAIDs, which reduce inflammation, are associated with reduced ovarian cancer risk?
A. That's my understanding.
Q. Wouldn't you expect, if your theory of inflammation is correct, that there would be consistency among the NSAID studies and that they would be consistently associated with reduced ovarian cancer risk?
A. I'd have to review those studies in more detail. I don't know what the doses of the NSAIDs were, how chronically they were used, whether they started at the time the chronic inflammation started or later.
Q. Would you agree that the literature that you cite and that you rely upon for your inflammation theory cites and just shows inflammation, not chronic inflammation, leading to cancer?
MS. O'DELL: Object to the form.
THE WITNESS: I'm talking about chronic inflammation, to be clear.
BY MR. ZELLERS:
Q. Let's take a quick look at your report.

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Page 4, you cite Eberl 1948, Redic 1988, and 1993 NTP study of rats and mice for the proposition that talcum powder is known to elicit an inflammatory response in animals and humans. Is that right?
A. Yes.
Q. Those studies just show an acute inflammatory response; is that right?
MS. O'DELL: Object to the form.
THE WITNESS: I don't recall that, but...
BY MR. ZELLERS:
Q. Well, are you familiar with the FDA's 2014 response to the citizens petition which we talked about earlier?
A. Yeah. Let me pull that out again.
Q. Sure. Do you have that available?
A. There's an exhibit here.
Q. I have it as Exhibit 19.
Do you see that -- do you have that in front of you?
A. I have the exhibit.
Q. So go to page 3, where the authors talk about the toxicologic findings.
Do you see that?
A. I'll get there in a second.

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Q. Sure.
Can I ask you a question?
A. Just give me one minute, please.
Okay.
Q. The FDA, in reviewing the toxicology findings and specifically commenting on the 1993 National Toxicology Program, published a study, they state -- and I'm reading now the last paragraph (as read):
"The study lacks convincing scientific support because of serious flaws in its design and conduct, including the investigators used micronized talc instead of consumer-grade talc, resulting in the experimental protocol not being reflective of human exposure conditions in terms of particle size."
Did I read that correctly?
A. Well, yes. But that's taken out of context to what's above here from the NTP report.
Q. Have you made a determination in this case about the size of the particles in talcum powder products?
A. They vary in size, from my understanding.

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Q. But the FDA noted -- and I'm looking at page 4 -- that (as read):
"The investigators conceded that they had problems with the aerosol generation system and that the study did not include positive and negative dust controls."
Is that right?
A. That's what it says.
Q. The FDA went on to conclude that (as read):
"In light of these shortcomings, a panel of experts at the 1994 ISRTP/FDA workshop declared that the 1993 NTP study had no relevance to human risk."
Did I read that correctly?
MS. O'DELL: Object to the form.
THE WITNESS: You read that correctly, and this -- that study was -- that workshop was convened a decade before this letter was written. There was definitely more information available that the FDA, once again, chose to not include or ignore.
BY MR. ZELLERS:
Q. Well, let's take a look at just a couple of the studies that you refer to in your report.

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You cite to the Buz'Zard 2007 study; is that right?
A. Yes.
Q. You rely on the Buz'Zard study to support your view that talcum powder causes chronic inflammation that leads to ovarian cancer. This is page 4 of your report, second-to-last paragraph.
A. Yes. I'm trying to pull out the Buz'Zard paper here.
Q. Do you need me to give it to you, or do you have it in front of you?
A. I have it, sir.
Q. All right. So this study was conducted in a nutritional lab, not a cancer lab; is that right?
A. Yes.
Q. The purpose of the study was to assess whether there was a certain effect from pine bark supplements; is that right?
A. There was an effect to neutralize the impact of talcum powder.
Q. Did you consider the type of cells that were evaluated in the Buz'Zard study?
And let me make it easy for you. The Buz'Zard study used immortalized cells; is that right? I'm looking at the second page, left column, "Cell

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culture and treatment."
A. I'm trying to find where they talk about human origin. Temperatures. Immortalized, yes. Normal ovarian epithelium and normal granulosa cells. It's not just generic immortalized cells.
Q. But the study used immortalized cells; is that correct?
A. Immortalized ovarian cells.
Q. Did you investigate whether the ovarian cells that they used were genetically altered?
A. Did I investigate whether they were genetically altered?
Q. Yes.
A. I had no opportunity to investigate that question.
Q. If the Buz'Zard study used genetically altered ovarian cells that did not have the p53 protein, would that affect your analysis of Buz'Zard?
A. I would have to turn to a molecular biologist to tell me what impact that might have had on the impact of this study.
Q. Well, you yourself, as we talked about in the very beginning today in one of your early publications, a cell missing the p53 protein is not a normal human ovarian cell; is that right?

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MS. O'DELL: Object to the form.
THE WITNESS: No, that's not what we were talking about this morning in the one 1993 study that I was a coauthor on. P53 mutation is what we were talking about.
BY MR. ZELLERS:
Q. Right. Well, looking at the Figure 3 of the Buz'Zard study 2007, "The inflammatory response does not increase with increasing doses of talcum powder."
Is that right?
MS. O'DELL: Object to the form.
THE WITNESS: It does up to a point.
BY MR. ZELLERS:
Q. Then stops; is that right?
A. That's right. And then it goes down, probably because the talcum powder was killing the cells.
MR. ZELLERS: Move to strike as nonresponsive.
BY MR. ZELLERS:
Q. In fact, the study shows that higher doses of talcum powder are associated with lower ROS generation; is that right?
MS. O'DELL: Object to the form.
THE WITNESS: That's what it says.

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BY MR. ZELLERS:
Q. Saed. You were citing the Saed studies, both 2018, and now the Harper and Saed 2009 -- strike that -- 2019 abstract; is that right?
A. Repeat the first one.
Q. Sure. You're relying, in part, for your inflammation theory on Saed 2018, that chapter, and the Harper and Saed 2019 abstract; is that right?
MS. O'DELL: Object to the form.
THE WITNESS: I'm relying on a paper -- a review paper published in Gyn Oncology in 2017. Is that what you're talking about?
BY MR. ZELLERS:
Q. Well, I thought Saed that you cite in your paper -- or your report -- was Saed 2018 and Harper and Saed 2019.
Are you relying on a Saed 2017 paper as well?
A. There's a review paper, "Updates on Oxidative Stress in Pathogenesis of Ovarian Cancer" that I am familiar with and is a very nice review paper describing oxidative stress and gene mutation.
Q. Well, let me ask you a --
A. But there's two other abstracts here that I think you're talking about.

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Q. Do you know that Dr. Saed is a paid expert for the plaintiffs' lawyers in this litigation?
A. No.
Q. Did you consider that fact in evaluating Dr. Saed's work?
A. I believe he's an honest scientist and is doing good scientific work.
Q. What is your basis for concluding that he's an honest scientist?
A. He has a good reputation in the gynecologic oncology community. He's published peer review publications that have been -- undergone critical peer review.
Q. Did Dr. Saed, in any of the publications that you have reviewed -- 2017, 2018, and 2019 -- disclosed that he's a paid expert for the plaintiff lawyers in this litigation?
MS. O'DELL: Object to the form.
THE WITNESS: Not exactly in those words.
BY MR. ZELLERS:
Q. Have you spoken with Dr. Saed?
A. No. I've never met him.
Q. Have you ever requested any information from Dr. Saed?

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A. No, I have not.
Q. The Saed study looked at immortalized cell lines; is that right?
MS. O'DELL: Which study are you referring to?
MR. ZELLERS: I'm referring to the 2018 and 2009 publications that you have referenced with the doctor.
MS. O'DELL: You said 2009 --
MR. ZELLERS: I'm sorry. 2019. Excuse me.
THE WITNESS: Just to be clear, just so we know the authors, so you're talking about Fletcher and Saed, the abstract?
BY MR. ZELLERS:
Q. I was referring to what you cite and reference in your report, which, at least in part, is Saed 2018 and Harper and Saed 2019.
Did you review those studies and are you relying, at least in part, on those studies?
A. Those studies and then with the subsequent full-length manuscript by Dr. Saed.
Q. All right. And you're aware that Dr. Saed looked at immortalized cell lines; is that right?
A. That is about the only way to do that kind of

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research, is with immortalized cells.
Q. Are you aware that Dr. Saed has testified that the cells were modified with a virus to make them undergoing -- strike that -- to make them keep undergoing division in vitro?
A. I was not aware of that, but it may be a laboratory technique that's necessary to do continuous studies on the same cell line.
Q. Are you aware that Dr. Saed testified that the p53 gene was turned off in those cells?
MS. O'DELL: Object to the form.
THE WITNESS: I was not aware of his testimony at all. I've not read his deposition.
BY MR. ZELLERS:
Q. What methodology did you use to apply the Saed results to normal cells in actual organs?
MS. O'DELL: Object to the form.
THE WITNESS: I think this is the best one can do, I presume -- I'm not a laboratory scientist, but the best they can do to replicate in vitro the impact of talcum powder on ovarian cells.
BY MR. ZELLERS:
Q. Can you cite any data showing that the concentrations of exposure used in the Saed study are the same as would be encountered in cosmetic use?

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MS. O'DELL: Object to the form.
THE WITNESS: I think we don't know how much talcum powder gets to the ovary.
BY MR. ZELLERS:
Q. Can you cite any data showing that the level of concentration of exposure used in the Saed study has ever occurred in women with perineal talc use?
A. I think that's an unknown answer.
Q. Do you know what SNPs are, S-N-P-S?
A. Yes. Single-nucleotide polymorphisms.
Q. The Saed abstract and article looked at single-nucleotide polymorphisms, or SNPs; is that right?
A. That's correct.
Q. They are changes to the individual building blocks of DNA; is that right?
A. Yes.
Q. SNPs can be caused by a number of agents or factors; is that right?
A. I believe so.
Q. Most SNPs have no effect on health or development; is that right?
MS. O'DELL: Object to the form.
THE WITNESS: Individual SNPs. So SNPs do represent a gene mutation, and they do have impact

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on the carcinogenesis, if you will, or development of cancer. Not in all cases.
BY MR. ZELLERS:
Q. What evidence do you have that the SNPs that Dr. Saed observed are associated with ovarian cancer?
A. We see that this chronic inflammation caused by talcum powder in his laboratory is creating SNPs, gene mutations. Gene mutations then become cancer.
Q. What studies can you cite that show that those SNPs have a statistically significant association with ovarian cancer?
MS. O'DELL: Object to the form.
THE WITNESS: I would have to return to the literature. There's a broad literature about SNPs that are more than the laboratory right now. But the combination of different SNPs is recognized as causing cancer.
I don't know the specific SNPs that you're referring to.
BY MR. ZELLERS:
Q. Other SNPs have no effect on health or development; correct?
A. Some.
MS. O'DELL: Object to the form.

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BY MR. ZELLERS:
Q. Oxidative stress, would you agree that reactive oxygen species are a normal part of cell physiology?
A. To some degree.
Q. Do all substances that cause oxidative stress also cause cancer?
A. No.
Q. Does the presence of oxidative stress in tissue indicate that cancer will develop in that tissue?
A. It can develop in that tissue.
MS. O'DELL: Excuse me, Mike. Whenever you get to a breaking -- stopping point, we've been going about an hour and 40 minutes, I think, something like that.
MR. ZELLERS: Sure. Let me just finish a couple of questions here.
BY MR. ZELLERS:
Q. The presence of oxidative stress in a tissue may or may not indicate that cancer will develop in that tissue; is that fair?
A. Yes, that's correct.
Q. If exposure to a substance causes oxidative stress in a certain tissue, does that mean that the

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substance will cause oxidative stress in all types of tissues?
A. Not necessarily.
Q. Does the body have protective mechanisms that can limit tissue damage from oxidative stress?
A. Yes.
Q. What publications indicate that oxidative stress is involved in the development of ovarian cancer?
A. We're again talking about the evidence that there's gene mutations being caused by oxidative stress.
Q. Can you cite to me a publication?
A. That results in ovarian cancer?
Q. Yes.
A. No, I can't cite that to you. I can show you the laboratory evidence that's leading to that conclusion that it will happen one day.
MR. ZELLERS: Let's take a break.
THE VIDEOGRAPHER: Going off the record at 3:22 p.m.
(Recess taken from 3:22 p.m. to 3:38 p.m.)
THE VIDEOGRAPHER: Back on the record at 3:38 p.m.

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BY MR. ZELLERS:
Q. Dr. Clarke-Pearson, are you familiar with the term "confounding"?
A. Yes.
Q. That's where the presence of another association confuses the relationship between the exposure and disease being studied; correct?
A. That sounds like a reasonable definition.
Q. For example, if you're studying the association between coffee and pancreatic cancer, you need to be mindful of whether cigarette smoking is more common in coffee drinkers than in the rest of the population; correct?
A. And if there's some synergism between the two.
Q. Cigarette smoking could be a confounder in that situation; is that right?
A. Yes.
Q. Because if more coffee drinkers are smokers than non-coffee drinkers, an association between coffee drinking and pancreatic cancer might be due to the smoking, not the coffee drinking; correct?
MS. O'DELL: Object to the form.
THE WITNESS: That's where a researcher would need to control for those variables.

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BY MR. ZELLERS:
Q. Confounding can distort results in epidemiologic studies; is that right?
A. Yes.
Q. You agree that residual confounding is possible in every observational study; correct?
A. I'm not sure I understand what "residual confounding" is.
Q. Well, residual confounding is confounding that remains even after you have controlled for known confounders.
MS. O'DELL: Object to the form.
THE WITNESS: So let me read your question.
BY MR. ZELLERS:
Q. Or I can ask it again.
A. Okay.
Q. I'll ask it again.
You agree that residual confounding is possible in every observational study; correct?
MS. O'DELL: Object to the form.
THE WITNESS: That is possible.
BY MR. ZELLERS:
Q. You agree that it's possible that unmeasured confounders may be present in every observational

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study; correct?
MS. O'DELL: Objection to form.
THE WITNESS: Yes, that's possible.
BY MR. ZELLERS:
Q. It's impossible to say that all known and unknown confounding factors have been controlled for in any given study; is that right?
MS. O'DELL: Object to the form.
THE WITNESS: That's why we do randomized control trials if possible.
BY MR. ZELLERS:
Q. Many new factors possibly involved in ovarian cancer are just being published in the literature; is that right?
MS. O'DELL: Object to the form.
THE WITNESS: What's being -- what I was referring to as new factors are really the biological mechanisms by which ovarian cancer occurs.
BY MR. ZELLERS:
Q. Well, through time, there have been different factors or potential factors involved in ovarian cancer; is that right?
MS. O'DELL: Object to the form.
THE WITNESS: Yes.

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BY MR. ZELLERS:
Q. Some of those are borne out and some are not; is that right?
A. I'm not sure what you mean --
MS. O'DELL: Object to the form.
THE WITNESS: -- by factors aren't borne out.
BY MR. ZELLERS:
Q. Well, at one point, was it thought that a mumps virus was a potential viral etiology of ovarian cancer?
A. Not that I'm aware of. When was that?
Q. You're not aware of that?
A. I'm not aware of it.
Q. All right. Well, how about Chlamydia infection, a history of Chlamydia infection and a history of weight gain during adolescence are two recent examples of potentially new factors involved with ovarian cancer; correct?
MS. O'DELL: Object to the form.
THE WITNESS: Well, we just finished talking about pelvic inflammatory disease, and Chlamydia is a pelvic inflammatory disease, so that may be a specific new factor. But we already have accepted PID as a risk factor.

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Obesity in adolescence may or may not be. I'm not aware of the data on that.
BY MR. ZELLERS:
Q. Factors weren't controlled for, Chlamydia infection, history of weight gain, those are factors that were not controlled for -- strike that. Let me be more precise.
A history of Chlamydia infection and a history of weight gain during adolescence are two recent factors that are being discussed among the gynecologic oncology community; correct?
MS. O'DELL: Object to the form.
THE WITNESS: I'm not aware of the obesity in adolescence. It may be.
BY MR. ZELLERS:
Q. Those factors were not controlled for in any of the published talc ovarian cancer studies; correct?
A. That's correct.
Q. You rely on Terry 2013 in your report. It's part of your graph on -- or your table on page 7; is that right?
A. Yes.
Q. Terry 2013 did not adjust for hormone replacement therapy usage; is that right?
A. I would have to look to see what he did and

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didn't adjust for.
Q. Is that easy for you to do?
A. I'm sorry?
Q. Is that easy for you to do?
A. It's buried in here under fine print, I'm sure.
Q. Let me -- let me ask the question this way: If hormone replacement therapy is a risk -- well, strike that.
Is hormone replacement therapy a risk factor for ovarian cancer?
A. We believe it is.
Q. If Terry 2013 -- and I'm asking you to assume this.
If Terry 2013 did not account for that potential confounding factor, then we wouldn't know whether the odds ratio in the study would have been lower if the authors had made that adjustment; correct?
MS. O'DELL: Object to the form.
THE WITNESS: Or it may have been higher.
BY MR. ZELLERS:
Q. We don't know; correct?
MS. O'DELL: Object to the form.

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THE WITNESS: We don't know.
BY MR. ZELLERS:
Q. Asbestos. You're, as you've told us today, an expert in asbestos; is that right?
A. I feel comfortable talking about asbestos.
Q. You feel comfortable, as you told us and testified earlier, testifying as an expert on asbestos; is that right?
MS. O'DELL: Object to the form.
THE WITNESS: I don't think I said I was an expert in asbestos.
BY MR. ZELLERS:
Q. Well, on page 9 of your report, you say (as read):
"There are numerous reports in the medical literature of minerals similar to talc causing cancer. Probably the most significant example is asbestos and lung cancer/mesothelioma."
Is that right?
A. Yes. I'm trying to find where I say that. I -- it sounds perfectly right.
I'm sorry. I'm having a hard time finding it. I looked under -- which topic are you reading

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from?
Q. All right. You got page 9, under "Analogy"? Or --
A. Yes.
Q. "There are numerous reports in the medical literature of minerals similar to talc causing cancer. Probably the most significant example is asbestos and lung cancer/mesothelioma."
Did I read that correctly --
A. Yes.
Q. -- from your report?
A. That's correct.
Q. How is talc similar to asbestos?
A. First of all, the -- a number of components in talcum powder have carcinogens in them. There's evidence that we haven't talked about yet that Johnson & Johnson baby powder and Shower to Shower had asbestos in it, that fibrous talc is a carcinogen according to IARC.
And, in addition, heavy metals that are contained in Johnson & Johnson baby powder, two of them are considered carcinogens also.
MR. ZELLERS: Move to strike as nonresponsive.

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BY MR. ZELLERS:
Q. How is talc similar to asbestos?
A. Talc has fibrous talc in it. Assuming there's -- let me just make an assumption that there's no asbestos in talc. So that's what you're asking me about.
Q. I'm asking you --
A. A hypothetical that talc doesn't have -- talcum powder doesn't have asbestos in it.
Q. My question to you is that you state here that there are minerals similar to talc causing cancer. And what I want to know is how is talc as a mineral similar to asbestos?
A. Talc has a fiber in it. Fibrous talc is similar to asbestos.
Q. Can you be any more specific?
MS. O'DELL: Object to the form.
THE WITNESS: It's considered a carcinogen. It's a long bundle of fibers.
BY MR. ZELLERS:
Q. Talc is a long bundle of fibers?
A. Fibrous talc is.
Q. Well, I'm asking you about talc right now. Is talc different than fibrous talc?
A. If you are talking hypothetically about platy

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talc only --
Q. I'm talking about you as an expert and describing for us the differences in the minerals talc, fibrous talc, and asbestos.
A. So platy talc hypothetically is probably not like asbestos, but it contains fibrous talc, which is a long, elongated mineral that can act in the human body similar to asbestos.
Q. Can you be any more descriptive, or is that as far as you can go in terms of explaining how fibrous talc is similar to asbestos?
A. Both cause a chronic inflammation in normal tissues and then go on to cause oxidative stress and mutations.
Q. I'm talking more about the minerals. Can you be any more descriptive about how fibrous talc, the mineral, is similar to asbestos?
MS. O'DELL: Objection to form.
THE WITNESS: Pictures I've seen look like asbestos particles, and fibrous talc looked very similar.
BY MR. ZELLERS:
Q. What other minerals that are similar to talc cause cancer?
MS. O'DELL: Object to the form.

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THE WITNESS: I'm not aware of any.
BY MR. ZELLERS:
Q. Are your opinions in this case dependent on talcum powder containing asbestos?
A. No.
Q. Do you believe that talcum powder that does not contain asbestos causes ovarian cancer?
A. Yes.
Q. If your -- if your assumption about contamination of talcum powder products with asbestos were not true, would that change your opinion in this case?
A. No.
MS. O'DELL: Object to the form.
BY MR. ZELLERS:
Q. Is it fair to say that you have not made any independent determination that the Johnson's baby powder and talcum powder products are contaminated with asbestos?
MS. O'DELL: Objection to form.
THE WITNESS: The only determination I've had is the evidence that I've seen.
BY MR. ZELLERS:
Q. You don't have the personal expertise to make that determination; is that right?

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A. I have the personal expertise to read reports from experts and --
Q. Do you have the personal expertise to do the testing necessary to determine whether or not talc is contaminated with asbestos?
A. No, I do not.
Q. You're relying on the reports of Longo for that information; is that right?
MS. O'DELL: Object to the form.
THE WITNESS: And I think also testing that was performed by Johnson & Johnson, reported in the John Hopkins deposition.
BY MR. ZELLERS:
Q. Well, you're talking about the two exhibits that you looked at, one exhibit in John Hopkins' deposition and one exhibit in Julie Pier deposition; is that right?
A. Yes.
Q. You were given those documents by Dr. Thompson and counsel for plaintiffs; is that right?
A. Or by Ms. O'Dell, I'm not sure who.
Q. Or by Ms. O'Dell. I'll put her in the counsel of plaintiffs.
You did not undertake a review of the

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literature on the topic of the alleged presence of asbestos in talcum powder; is that right?
MS. O'DELL: Object to the form.
THE WITNESS: The literature?
BY MR. ZELLERS:
Q. You're relying for their -- strike that.
For the proposition that there is asbestos in the Johnson's baby powder and Shower to Shower product, your reviewing on the documents you were provided by counsel, the exhibit from John Hopkins' deposition, the exhibit from Julie Pier, and from the selected company documents they provided to you; correct?
A. I'm also relying on a publication by A.M. Blount.
Q. That's what we identified earlier; is that right?
A. I believe so.
Q. The A.M. Blount article deals with mesothelioma, not ovarian cancer; is that right?
MS. O'DELL: Objection to form.
THE WITNESS: It talks about the presence of asbestos in talcum powder.
BY MR. ZELLERS:
Q. Do you know that the deposition exhibits that

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you were given -- the exhibit to John Hopkins' deposition and the exhibit to Julie Pier's deposition -- that they were tables and exhibits that were created by the plaintiff attorneys?
MS. O'DELL: Objection to form.
THE WITNESS: I'm not aware of how these tables were created.
BY MR. ZELLERS:
Q. Do you know where the data in those exhibits came from?
A. I do not.
Q. Are you -- strike that.
Have you made any effort to investigate any alternative explanations for the data in those charts? And I'm talking about the Hopkins and Pier deposition exhibits.
A. No.
Q. If scientists with Johnson & Johnson companies and Imerys scientists say that those tests don't actually show asbestos, you have no expertise to dispute that personally, do you?
MS. O'DELL: Object to the form.
THE WITNESS: Personally, no.
BY MR. ZELLERS:
Q. Have you looked at the evidence or been

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provided with the evidence of Johnson & Johnson companies and Imerys that, in fact, those tests do not show asbestos?
MS. O'DELL: Object to the form.
THE WITNESS: You're referring to the charts that I have?
BY MR. ZELLERS:
Q. Yes.
A. I'm not aware of that.
Q. Have you confirmed that any of the talc samples mentioned in those charts, the two exhibits of Hopkins deposition and Pier deposition, were actually from talc that was used in body powder?
A. I believe the testing that was reported in Hopkins was from Johnson & Johnson.
Q. Number one, have you confirmed that any of the talc samples mentioned in those charts were actually from talc that was used in body powder?
MS. O'DELL: Objection to form.
THE WITNESS: I can't confirm that.
BY MR. ZELLERS:
Q. You realize that the vast majority of talc isn't used for body powder; correct?
MS. O'DELL: Objection to form.
THE WITNESS: I don't know.

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BY MR. ZELLERS:
Q. Did you consider any testing of Johnson & Johnson or Imerys that found no asbestos in the talcum powder?
A. I presume there is. The report by Dr. Longo didn't show it in every single sample.
Q. Well, did you consider -- did you review any of that testing of either Johnson & Johnson companies or Imerys that found no asbestos?
A. I was not aware of any data on that to that point.
Q. Were you provided that data or those test results by counsel for plaintiffs?
A. No.
Q. Have you reviewed the FDA's testing of talcum powder products?
A. You'd have to show me that evidence.
Q. Do you recall, sitting here, whether or not you have been provided with the FDA's testing of talcum powder products?
A. I believe I've seen it.
Q. Have you made any effort -- well, strike that.
The FDA's testing, do you recall whether it found asbestos or did not find asbestos?

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A. My recollection was, whatever technique they used, they didn't find asbestos.
Q. Have you made any effort to quantify the amount of any alleged contaminant in the Johnson's baby powder products?
MS. O'DELL: Objection to form.
THE WITNESS: What contaminant are you talking about?
BY MR. ZELLERS:
Q. Well, let's start with asbestos.
A. I haven't made any effort to quantify aside from what's in the reports.
Q. Have you made any effort to quantify the trace amounts of heavy metals that you contend are in the baby powder?
A. I have not tried to quantitate that except for what's in the reports.
Q. Have you attempted to quantify in any manner the fragrance chemicals that you believe are contained in the baby powder?
MS. O'DELL: Objection to form.
THE WITNESS: The fragrance chemicals that I know are contained in the baby powder?
BY MR. ZELLERS:
Q. Well, you don't really know if any fragrance

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chemicals are contained in the baby powder. You have reviewed some documents and materials prepared by others which talk about that; right?
A. Yes.
Q. All right. Do you have an opinion on what type of asbestos, if any, is in the Johnson's baby powder?
A. Looking at the reports, there are several types.
Q. Tell us what types you believe -- what types of asbestos are found or -- strike that.
What types of asbestos are found in the baby powder?
A. So this is from the Hopkins Report. Tremolite. Crystalline. Some more crystalline. Crystalline. Crystalline. Tremolite. Actinolite. Actinolite.
Would you like me to go on?
Q. Well, you're just reading down from the Hopkins, Exhibit 47; is that right?
A. That's correct.
Q. Do you know what type of asbestos is most commonly associated with ovarian cancer?
MS. O'DELL: Object to the form.
THE WITNESS: I think they all are.

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BY MR. ZELLERS:
Q. That's your belief? That all types of asbestos are equally associated with ovarian cancer?
A. I think they're all carcinogens.
Q. Am I correct that, at least as you sit here, you believe that all forms of asbestos are associated with ovarian cancer?
A. There's never been a randomized trial exposing women to different forms of asbestos to determine whether one is more carcinogenic than the other.
Q. So your answer is yes; is that right?
MS. O'DELL: Object to the form.
MS. BOCKUS: I was going to object to his prior answer as nonresponsive.
THE WITNESS: Your question was, "Am I correct?"
BY MR. ZELLERS:
Q. What I want to know --
A. Do I believe that all forms of asbestos are associated with ovarian cancer? And the answer is yes.
Q. Is there a particular type of asbestos that is primarily associated with ovarian cancer?
MS. O'DELL: Objection. Asked and

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answered.
THE WITNESS: Not that I'm aware of.
BY MR. ZELLERS:
Q. What dose of asbestos is associated with ovarian cancer?
A. We don't know. Possibly any dose.
Q. What type of ovarian cancer is asbestos associated with?
I guess that goes back to the answer before. You don't know. Is that right?
MS. O'DELL: Objection to form. That's not what he said.
THE WITNESS: It's associated with epithelial ovarian cancer.
BY MR. ZELLERS:
Q. Does the type of ovarian cancer vary based on the type of asbestos?
MS. O'DELL: Objection. Asked and answered.
THE WITNESS: I don't think anybody knows that.
BY MR. ZELLERS:
Q. You've looked at studies that have explored the potential link between asbestos and ovarian cancer; is that right?

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A. Yes.
Q. Are you familiar with the limitations of that research?
MS. O'DELL: Objection. Vague.
THE WITNESS: I'm not quite sure --
BY MR. ZELLERS:
Q. I'm sorry. Did you finish?
A. Yes.
Q. One of the papers you looked at -- and I think it's contained in one of your folders -- was the Reid 2011 paper. Is that right?
A. Yes.
Q. That was research on the potential relationship between asbestos and ovarian cancer. One of the limitations as discussed by Reid is that there's a very small number of cases.
Is that right?
MS. O'DELL: Object to the form.
THE WITNESS: I believe so.
BY MR. ZELLERS:
Q. Is it true that most, if not all, of the studies that you have reviewed with respect to asbestos and ovarian cancer involve occupational exposure?
MS. O'DELL: Object to the form.

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THE WITNESS: That's correct.
BY MR. ZELLERS:
Q. Did any of the nonoccupational asbestos studies reach statistical significance?
A. No.
Q. Do you know how many women have been studied in nonoccupational settings?
A. In this particular study, it looks like Italian wives of asbestos factory workers would be in nonindustrial settings is 1780 women.
Q. Are you aware of the difficulties that have existed over time in distinguishing between peritoneal mesothelioma and ovarian cancer?
A. I'm aware that there are some uncertainty in some pathologic diagnoses, yes.
Q. Those difficulties potentially affect the reliability of the studies; is that right?
A. Well, I think both epithelial ovarian cancer and mesothelioma of the ovary or peritoneum are both malignancy.
Q. Well, the studies have acknowledged that it's difficult to distinguish between the two, between peritoneal mesothelioma and ovarian cancer; is that right?
A. Pathologically, that's correct.

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Q. And the Reid study, again, makes that finding. On the first page, in the right-hand column, Number 2, "Difficulties with Diagnosis"; is that right?
A. Yes.
Q. Have the studies addressed confounding and independent risk factors?
MS. O'DELL: Object to the form.
THE WITNESS: Well, I'm certain that -- I would be quite confident that they didn't evaluate these women, whether they had a BRCA1 or 2 mutation or not, and other risk factors were not included.
BY MR. ZELLERS:
Q. Well, Camargo 2011. That's another study that you put in one of your folders in preparation for today; is that right?
A. Yeah.
Q. That study acknowledged an inability to account for nonoccupational risk factors for ovarian cancer other than age; is that right?
A. Yes.
Q. These researchers conducted a meta-analysis to evaluate the association between asbestos and ovarian cancer; is that right?
A. Yes.

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Q. And they acknowledge, as we spoke just a moment ago, that they could not account for nonoccupational risk factors for ovarian cancer other than age; is that right?
A. I believe so.
Q. Also looking at Camargo, wouldn't you expect to find higher rates of other cancers in women using talc, like mesothelioma, if they are being exposed to substantial amounts of asbestos?
MS. O'DELL: Object to the form.
THE WITNESS: They would be -- they would have to inhale it to a quantity enough to cause mesothelioma of the lung.
BY MR. ZELLERS:
Q. Are women who use talc in the perineal region at greater risk of mesothelioma?
A. Not that I'm aware of.
Q. Are women who use talc in the perineal region at greater risk of asbestosis?
A. Not that I'm aware of.
Q. If there was more asbestos in talcum powders in the 1970s, shouldn't we have seen higher rates of ovarian cancer in the earlier studies?
MS. O'DELL: Object to the form.
THE WITNESS: I think getting back to your point about confounding issues, the risk factors in the 1970s above and beyond exposure to talc were not always controlled for. I think we know more about that today in ongoing studies.
BY MR. ZELLERS:
Q. You'd agree that exposure to asbestos through the perineal cosmetic talc use, assuming that talc contains asbestos fibers, is different from the heavy occupational exposure that's primarily been researched; is that right?
MS. O'DELL: Object to the form.
THE WITNESS: Yes, I would agree with that.
BY MR. ZELLERS:
Q. Is the asbestos that women are exposed to from using cosmetic talc qualitatively the same as the raw asbestos encountered at a factory, if you know?
MS. O'DELL: Object to the form.
THE WITNESS: The raw asbestos encountered at a factory before it's processed?
BY MR. ZELLERS:
Q. Yes.
A. I don't know the answer to that.
Q. Do you know what a cleavage fragment is?
A. It's part of platy talc.

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Q. Do you know how a cleavage fragment differs from an asbestos fiber?
A. It has to do with the size of the fiber.
Q. Do you have any opinions about cleavage fragments in this case?
A. What case are we talking about?
Q. You serving as an expert witness in the --
A. I guess I think of a case as a patient.
Q. Well, you're here today talking generally about the risk of ovarian cancer from talcum powder use; is that right?
A. Yes.
Q. Do you intend to express any expert opinions in this matter about cleavage fragments?
MS. O'DELL: Objection to form.
THE WITNESS: If asked.
BY MR. ZELLERS:
Q. Okay. What opinions do you have about cleavage fragments? And, specifically, how does a cleavage fragment differ from an asbestos fiber?
A. So it has to do with the ratio of length to width, and a cleavage factor has a less than 6:1 proportion.
Q. Anything else?
A. You were asking about cleavage fragments?

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Q. Yes. And I'm asking how it differs from an asbestos fiber --
A. Asbestos needle is longer. It's either a ratio of 6:1 up to less than 15:1.
Q. Anything else?
A. And then fibers are considered greater than 15:1 ratio.
Q. Asbestos fibers or cleavage fragments?
A. Asbestos fibers.
Q. How does a cleavage fragment differ from fibrous talc?
A. I'm not sure I know the difference.
Q. Does it make a difference to your theory and your opinions if it turns out that talc contains cleavage fragments of nonasbestiform amphiboles instead of asbestiform amphiboles?
MS. O'DELL: Objection.
THE WITNESS: I'm going to have to read your question.
BY MR. ZELLERS:
Q. Sure. And if you don't have opinions, that's okay. I'm just trying to find out what you have opinions about.
A. No, I don't have an opinion.
Q. You don't have opinions about whether or not

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regulatory action in this area rejects the idea that science has established that cleavage fragments or nonasbestiform amphiboles pose the same risk as asbestos; correct? You leave that to other experts to address?
A. The regulatory portion, yes.
Q. How, if at all, did you factor the difference between asbestiform and nonasbestiform minerals into your analysis of the relationship between talcum powder use and ovarian cancer?
MS. O'DELL: Objection to the form. Compound.
You may answer the question if you understand it.
THE WITNESS: Well, I'm quite certain, based on IARC, that asbestiform minerals are carcinogenic.
BY MR. ZELLERS:
Q. That is your answer to my question?
A. Yes.
Q. All right. Fragrance chemicals and heavy metals, you're aware those are addressed in Dr. Crowley's report; is that right?
MS. O'DELL: Objection. Form.
THE WITNESS: Yes. I don't have that

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in front of me, though.
BY MR. ZELLERS:
Q. You're not expressing opinions in this case on fragrance chemicals and heavy metals and any association fragrance chemicals and heavy metals may have on ovarian cancer; correct?
MS. O'DELL: Objection. Form.
THE WITNESS: No. I am expressing an opinion about that.
BY MR. ZELLERS:
Q. What research have you done with respect to the fragrance chemical and trace amounts of heavy metals that are contained in the talcum powder?
MS. O'DELL: Objection to the form. Compound.
THE WITNESS: It's my opinion that talcum powder causes ovarian cancer, that talcum powder contains platy talc, fibrous talc, asbestos, heavy metals -- three of them -- and fragrances.
I'm not necessarily saying one of that list is causing the cancer. It's the talcum powder -- the baby talc -- baby powder and the Shower to Shower -- that's causing the ovarian cancer.
BY MR. ZELLERS:
Q. I understand that, and I think I've asked you

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my questions with respect to that.
What I'm asking about now is whether or not you have made a separate analysis as to whether one or more of the fragrance chemicals or one or more of the trace heavy metals that have been reported to be contained in talcum powder, whether those are causally associated or a causal factor for ovarian cancer?
A. In combination with the commercial product called baby powder and Shower to Shower, I think they all contribute to the outcome, which is ovarian cancer.
Q. Are you relying on any scientific literature to support your opinion that some of the chemicals in Johnson's baby powder cause ovarian cancer?
MS. O'DELL: Object to the form.
THE WITNESS: We know that they can be carcinogenic.
BY MR. ZELLERS:
Q. With respect to ovarian cancer.
A. Not specifically to ovarian cancer. We haven't studied that.
Q. Do you have any evidence that the fragrance chemicals and trace heavy metals contained in Johnson's baby powder have been tested in human beings and found to cause inflammation?

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A. I'm not aware of those studies.
Q. Is there any epidemiology, human studies, substantiating the theory that fragrance ingredients can cause ovarian cancer?
A. Fragrance ingredients by themselves?
Q. Yes.
A. I'm not aware of any study that's evaluated that.
Q. Is there any epidemiology study substantiating the theory that fibrous talc is carcinogenic?
A. IARC claims it is carcinogenic.
Q. That it causes ovarian cancer, specifically?
A. I believe so.
Q. You'd defer to IARC on that; is that right?
MS. O'DELL: Object to the form.
THE WITNESS: Yes.
BY MR. ZELLERS:
Q. Is there any epidemiology substantiating the theory that exposures to trace amounts of heavy metals, allegedly, or that you believe are contained in the Johnson's baby powder can cause ovarian cancer?
A. I'm not aware that anybody's done a randomized trial in human beings with carcinogen -- carcinogenic heavy metals to evaluate whether ovarian

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cancer or any other cancer might occur.
Q. Well, aside from a randomized clinical trial, are you aware of any other epidemiology substantiating the theory that exposures to trace amounts of the heavy metals that are reported to be in the Johnson's baby powder can cause ovarian cancer?
MS. O'DELL: Object to the form.
THE WITNESS: I don't think that anybody's ever studied that as a separate entity of metals only exposed to the ovary.
BY MR. ZELLERS:
Q. You have no evidence that the blood or tissue levels of any trace heavy metals are higher in genital talc users as compared to nonusers; is that right?
A. That's correct.
Q. Are your opinions in this case depending on talc containing carcinogenetic [sic] metals?
A. Not necessarily.
Q. Are your opinions in this case dependent on talc containing carcinogenetic [sic] fragrances?
A. Not necessarily.
Q. Do you have any opinions or knowledge as to the concentration of each of the fragrance chemicals that are contained in Johnson's baby powder?
A. No.

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Q. Or Shower to Shower?
A. No.
Q. You've not done any independent testing of that; correct?
A. That's correct.
Q. How, if at all, did you factor the dose fragrances and heavy -- or trace heavy metals into your analysis of the potential relationship between those compounds and ovarian cancer?
A. I didn't factor in.
Q. Let me ask you a couple of questions about the Health Canada assessment and the Taher article. Those are new materials that you reviewed between the time of your report and appearing here today; is that right?
A. That's correct.
Q. Have you read the draft Health Canada risk assessment -- I'll provide you with a copy so we know what we're speaking of.
(Exhibit No. 29 was marked for identification.)
MR. ZELLERS: Deposition Exhibit 29 is the draft Health Canada decision framework -- strike that.
Exhibit 29 is the Health Canada Decision-Making Framework for Identifying, Assessing,

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and Managing Health Risks.
Is that not what he's reviewed?
MS. O'DELL: If you're handing him that and suggesting, that's not the health assessment that he's reviewed.
MR. ZELLERS: So do we have the health assessment here? And, if not, we can just identify it. But I do want to ask him a few questions about the --
MS. O'DELL: I do think we have it here. But, if you're going to ask him questions, I would put it in front of him. So, if we don't have a hard copy, I'm happy to put my electronic copy in front of him.
MR. ZELLERS: Well, please put whatever you think you need to put in front of the witness so he can answer a couple of questions about the Health Canada risk assessment.
MS. O'DELL: Sure. Give me just a moment --
MR. ZELLERS: Sure.
MS. O'DELL: -- because the copy I have is marked up, and I know you prefer for me not to hand him my marked-up copy.
MR. ZELLERS: I would prefer that.

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MS. O'DELL: Doctor, if you want to just use my computer, feel free to --
THE WITNESS: Okay. I'm not real fast at running through a computer, but --
BY MR. ZELLERS:
Q. Hopefully, my questions will be pretty high-level.
You have in front of you the draft Health Canada risk assessment; is that right?
A. On my tablet, yes.
Q. Have you looked into what other public health authorities have had to say about talc and ovarian cancer?
A. Except for what the FDA has had to say.
Q. The answer is, no, other than with respect to what the FDA has said; is that right?
A. The answer is no.
Q. Why would you rely on Health Canada but not other public health organizations?
MS. O'DELL: Object to the form.
THE WITNESS: It's my understanding that this is very recent analysis of the issues regarding talcum powder and ovarian cancer and other harms.

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BY MR. ZELLERS:
Q. You understand it's a draft assessment; is that right?
A. That's correct.
Q. You understand that we're at the very beginning of the public comment period; is that right?
MS. O'DELL: Object to the form.
THE WITNESS: I don't know that.
BY MR. ZELLERS:
Q. Are you aware that Health Canada can take up to two years to take any action or no action at all?
MS. O'DELL: Object to the form.
THE WITNESS: I was not aware.
BY MR. ZELLERS:
Q. How did you come to learn of the Health Canada risk assessment?
A. It was brought to my attention by counsel.
Q. By counsel for plaintiffs; is that right?
A. That's correct.
Q. Were you involved in the risk assessment prior to its publication?
A. Was I involved?
Q. Yes.
A. No.
Q. Have you submitted any comments to Health

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Canada?
A. I wasn't aware -- as I said, I wasn't aware that there were comments that could be made.
Q. Outside of your litigation consulting work, do you generally rely on draft assessments by regulatory agencies?
MS. O'DELL: Object to the form.
THE WITNESS: I think it's something that's worth looking at. It doesn't necessarily sway my opinion, but could be useful additional information that might be cutting edge.
BY MR. ZELLERS:
Q. You don't cite or -- strike that.
You do not rely on draft regulatory assessments in your peer-reviewed publications and studies; is that right?
MS. O'DELL: Object to the form. Asked and answered.
THE WITNESS: Not usually, but don't know what -- there's information there. If there's information I can extract from a draft of something that's useful, I can use it.
BY MR. ZELLERS:
Q. Are you familiar with the precautionary principle?

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A. Slightly.
Q. Basically, that means taking a precautionary approach to decision-making that emphasizes the need to take timely preventative action even in the absence of a full scientific demonstration of cause and effect.
Does that sound right?
A. Sounds very reasonable, yeah.
Q. You understand that Health Canada may have made recommendations that are purely precautionary; is that right?
MS. O'DELL: Object to the form.
THE WITNESS: That's what I've read, yes.
BY MR. ZELLERS:
Q. I can go through the document for it if need be, but in the -- its publication -- I'll hand it to you -- which we've marked as Exhibit 29, it is captioned "Health Canada Decision-Making Framework for Identifying, Assessing, and Managing Health Risks."
Do you have that in front of you?
A. You've handed it to me, yes.
Q. If you go to page 5, Health Canada sets out the bases for its risk assessments; is that right?
A. Let me get to page 5 here.

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Q. Sure.
A. In the black box "Underlying Principles"?
Q. Yes, "Underlying Principles."
One of the underlying principles is "use a precautionary approach"; is that right?
A. That's what it says.
Q. If you go, then, to page 8, second paragraph, second sentence, where Health Canada sets forth "use of a precautionary approach," the second sentence reads (as read):
"A precautionary approach to decision-making emphasizes the need to take timely and appropriately preventative action even in the absence of a full scientific demonstration of cause and effect."
Did I read that correctly?
A. Yes, sir.
Q. So a recommendation by Health Canada does not require a finding of causation like is required in a court. Does that sound right based upon what we have reviewed here?
MS. O'DELL: Object to the form.
THE WITNESS: I'm not sure what the

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requirements are for court. I understand the precautionary portion here.
BY MR. ZELLERS:
Q. And you also understand that, with the use of a precautionary approach, that action can be taken even in the absence of a full scientific demonstration of cause and effect?
MS. O'DELL: Objection to form.
THE WITNESS: What action are you talking about?
BY MR. ZELLERS:
Q. Well, decision-making, any sort of assessment.
MS. O'DELL: Objection to form.
THE WITNESS: I'm still not understanding.
BY MR. ZELLERS:
Q. Sure. Health Canada --
A. Yes.
Q. -- does not need, in terms of its risk assessment, to have a full scientific demonstration of cause and effect?
A. I understand.
MS. O'DELL: Objection to form.

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BY MR. ZELLERS:
Q. All right. Thayer 2018, that's a new and additional meta-analysis that you have reviewed?
A. Yes.
Q. Let's mark Thayer 2018 as Deposition Exhibit 30.
(Exhibit No. 30 was marked for identification.)
BY MR. ZELLERS:
Q. And you can tell us if this is --
A. I've got a copy.
Q. Well, take, if you will, the court -- deposition exhibit number. Just put it in your pile there so we can make sure we all understand what we're talking about.
You have seen this review before; is that right?
A. Yes, I have.
Q. The Health Canada risk assessment that you looked at a few moments ago relies on this meta-analysis by Thayer and others; is that right?
A. That's my understanding. They may use other information too.
Q. Do you know whether or not Thayer 2018 has been peer-reviewed?
A. I'm not aware of that.

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Q. Do you know if it has been submitted for publication?
A. I do not know.
Q. How can you rely on the Health Canada risk assessment without assessing the quality of one of the major studies on which they rely?
MS. O'DELL: Objection to form.
THE WITNESS: And the major study you're referring to is Thayer?
BY MR. ZELLERS:
Q. Yes.
A. Let me read the first part of your question here.
So I'm not saying that I rely on the Health Canada risk for my total opinion. It's another piece of evidence and information that's helpful in me coming to my opinion. And this only supports my opinion.
Bradford Hill's breakdown is very similar to my opinion. I didn't see this before I created my opinion.
Q. Do you know if Thayer 2018 employed a reliable methodology?
A. I believe it's very similar to other methodology and systematic reviews and meta-analyses.

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Q. Did you have access to the appendices or supplemental tables referenced in the Thayer meta-analysis?
A. I did not.
Q. Do you know the source of funding for Thayer 2018 meta-analysis?
A. If it was listed on here, I should have picked it up. If not, then I don't know the answer to your question.
Q. Do you know the credentials of the authors of Thayer 2018?
A. None other than what are listed on the cover sheet of this paper.
Q. Do you personally know any of the authors of Thayer 2018?
A. No, sir.
Q. Do you know whether or not any of those authors have conflicts of interest or potential conflicts of interest?
A. Do not know.
Q. In Thayer 2018, the authors concluded that "The evidence suggests that asbestos contamination does not explain the positive association between perineal use of talc powder and ovarian cancer."
Is that right?

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MS. O'DELL: Mike, what page are you reading from?
MR. ZELLERS: Page 41, last sentence. So we're on Deposition Exhibit 30, the Thayer meta-analysis, page 41, last part.
MS. O'DELL: Thank you.
BY MR. ZELLERS:
Q. Doctor, I really just have a really simple question.
A. Okay.
Q. So the authors conclude -- or state that (as read):
"The similarity of findings between studies published prior to and after this point suggest asbestos contamination does not explain the positive association between perineal use of talc powder and risk of ovarian cancer."
Is that right?
MS. O'DELL: Object to the form.
THE WITNESS: That's what they say.
BY MR. ZELLERS:
Q. Do you disagree with the authors on that point?
A. I do not disagree with the author on that point.
Q. One of the Bradford Hill criteria that we've discussed is consistency; is that right?
A. Yes.
Q. Look at Thayer 2018. So Exhibit 30, page 25, Table 2.
Do you have that?
A. Yes.
Q. Table 2 is entitled "Summary of Evidence for Each of the Hill Criteria of Causation as Applied to Perineal Application of Talc and Ovarian Cancer."
Is that right?
A. I'm sorry. What were you reading -- where were you reading from?
Q. Sure. Table 2 on page 25 --
A. Right.
Q. -- is captioned "Summary of Evidence for Each of the Hill Criteria of Causation as Applied to Perineal Application of Talc and Ovarian Cancer."
A. Yes.
Q. And they kind of go through the same Bradford Hill factors that you do; is that right?
A. Yes.

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Q. Under "Consistency," they said that (as read):
"15 out of 30 studies reported positive and significant associations."
Is that right?
A. That's right.
Q. We're back to, similar with Langseth, half the studies showing significant associations and half the studies don't. Thayer reports that same findings here; is that right?
A. Yes, but not all studies have the same weight.
Q. And we've discussed that before; is that right?
A. Yes. I just wanted to bring it up again, since we're talking about that topic.
Q. Let's go to "no dose response." And that was your -- well, let me withdraw that statement.
Go to page 21, if you will, second paragraph, last few sentences.
Do you have that?
MS. O'DELL: What page are you on?
MR. ZELLERS: Page 21.

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BY MR. ZELLERS:
Q. The authors here in this section are discussing whether or not there is a dose response and dose response findings in the studies; is that right?
A. Yes.
Q. They conclude at the very end -- and I'm looking on page 21, the last sentence above 3.3.2 (as read):
"When conducted, findings from trend analyses were not consistent."
Do you see that?
A. Yes, I do.
Q. The authors recognize that there's no consistent dose response across studies, and you agree with that; is that right?
MS. O'DELL: Objection to form.
THE WITNESS: I think there's some evidence there's dose response. Some studies don't do enough to evaluate for dose response, especially the cohort studies that are pretty well destroyed back on page 43.
BY MR. ZELLERS:
Q. Some studies find dose response and some studies don't; correct?

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MS. O'DELL: Objection to form.
THE WITNESS: That's correct.
BY MR. ZELLERS
Q. And that's true of case-control studies; is that right?
A. Yes.
Q. I want to go back to a question I had asked you earlier.
When you do surgery and you see inflammation, would you agree that inflammation that you see is likely related to the cancer itself?
A. So let me clarify so we don't get confused.
The inflammation that I see is purely ascites. The rest -- which is fluid in the abdomen either caused by the cancer or by inflammation.
Q. The ascites can be caused by the cancer itself; correct?
A. Yes.
MR. ZELLERS: I have no further questions. Some of my colleagues may have questions for you. Thank you for your time.
THE WITNESS: Thank you.
MS. BOCKUS: Could we take a quick break so that we can change places?
MS. O'DELL: Sure.

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THE VIDEOGRAPHER: Going off the record at 4:36 p.m.
(Recess taken from 4:36 p.m. to 4:44 p.m.)
THE VIDEOGRAPHER: Back on the record at 4:44 p.m.
CROSS-EXAMINATION BY COUNSEL FOR THE DEFENDANT IMERYS
BY MS. BOCKUS:
Q. Doctor, I just want to be sure that what we have marked so far will provide us with copies of all of your handwritten notes.
A. Certainly.
Q. Okay. Are there some handwritten notes that are not on the table in front of you right now?
A. Yeah. There's some in these files and some -- like this, with sticky notes.
Q. And that's what I'm looking for. I want to make sure I get all your sticky notes and all of the notations that you have made in your review of the articles.
And so when we get -- it looks like there are two binders that have flags and that sort of thing in them. Are there notes in the binders that are over on the table?
A. No, ma'am.
Q. Okay. So other than the binders and the

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materials that are on the table, do you have handwritten notes somewhere else?
A. No.
Q. Earlier today, you were asked a question -- I think it was about the FDA letter -- and you thought you had some handwritten notes on that. Do you know where those might be?
A. I don't recall now. You know, it was a sticky note. Just what I've been trying to do is abstract these papers to a few facts that I think are important. It's not personal opinions or other things like that; it's just trying to move the conversation along.
Q. Would you agree that in general ovarian cancer is a disease of aging?
MS. O'DELL: Objection to form.
THE WITNESS: That is one of the risk factors, yes.
BY MS. BOCKUS:
Q. That very few women are diagnosed with ovarian cancer who are under 30 years of age; correct?
A. With epithelial ovarian cancer, yes.
Q. And that risk -- so the numbers are different depending which type of ovarian cancer you're talking about; correct?

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A. Yes.
Q. So confining it to epithelial ovarian cancer, that risk starts to rise in the 30s and rises even more in the 40s, 50s, and 60s; correct?
A. Yes, that's my understanding.
Q. And in the 60s, it kind of levels off --
A. In the 60s or 70s. I've forgotten what the curves look like exactly.
Q. And other than being female of a certain age, most patients who you see, you don't have any idea of what caused their ovarian cancer; correct?
MS. O'DELL: Object to the form.
THE WITNESS: Again, I get back to my theme about gene mutation. Something caused the gene mutation to cause that normal cell that's mutated now to become malignant.
BY MS. BOCKUS:
Q. Exactly. Somewhere along the aging process, perhaps, or through some exposure, there's been a gene mutation and -- well, let me stop there. Scratch all that.
It actually takes multiple gene mutations for a cancer to begin, does it not?
A. That's our understanding.
Q. Our understanding is that several things

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happen -- have to happen before a cancer cell is formed; correct?
A. That's our usual understanding of what the onset of cancer is.
Q. And our general understanding is that it takes decades for that to happen, generally speaking; correct?
A. It depends upon what the mutations are. A woman that's born with a genetic mutation of BRCA1, for example, already has some mutations. So that's why we believe they develop ovarian cancer at an earlier age. Just a couple more mutations, and then the ovarian cancer starts.
Whereas a woman that doesn't have a BRCA1 mutation, as she gets older, she obtains or gets mutations over time. And the longer you live, the more likely you are to have those mutations to become ovarian cancer.
Q. And one of the things that happens over time is our body's ability to fight off detected mutations decreases; correct?
A. Yes, in general.
Q. So back to my prior question, when patients come to you who have ovarian cancer, other than being female and over a certain age, are you ever able to

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tell them what caused the genetic mutation that caused their cancer?
MS. O'DELL: Object to the form.
THE WITNESS: Aside from the inherited BRCA mutations and Lynch syndrome, in general, no, we can't.
BY MS. BOCKUS:
Q. Would you agree that what we know today about what causes ovarian cancer is actually dwarfed by what we don't yet know about the cause of ovarian cancer?
MS. O'DELL: Object to form.
THE WITNESS: I think it's fair to say we know some risk factors.
BY MS. BOCKUS:
Q. But we're learning new risk factors and new genetic mutations all the time; correct?
MS. O'DELL: Object to the form.
THE WITNESS: In general, we're moving along those lines in research.
BY MS. BOCKUS:
Q. I just want to be clear. Is it your position that being powdered as an infant with talc increases that person's risk of being diagnosed with ovarian cancer as a woman?
A. I think it's the sustained exposure more than

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if an infant was just -- received talcum powder and then never continued to use it into her 20s, 30s, 40s, and 50s, my opinion would be that infant is not at particularly high risk.
Q. Is it your opinion that powdering one's baby with talcum powder increases the mother's risk of ovarian cancer?
MS. O'DELL: Object to the form.
THE WITNESS: So just -- just through inhaled? I believe that there's not enough evidence to say that.
BY MS. BOCKUS:
Q. Okay. And so fair to say that you're truly confining your opinion to the theory that talc can travel from the perineum to the ovary and cause ovarian cancer that way; is that correct?
A. And cause --
MS. O'DELL: Object to the form.
Excuse me.
THE WITNESS: -- cause chronic irritation and inflammation, yes.
BY MS. BOCKUS:
Q. In order for a cancer to be called a cancer, it has to evolve in such a way that it has limitless replicative potential; correct?

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MS. O'DELL: Object to the form.
THE WITNESS: I think cancers -- if I understand what you're saying, some cancers also replicate rapidly and then slow down and may be indolent for a period of time.
So the timeline of onset of cancer to death, which is, I guess, the timeline, can vary from one patient to another.
BY MS. BOCKUS:
Q. Cancer needs to develop the ability to evade apoptosis; correct?
A. I'm sorry?
Q. Evade apoptosis.
A. Yeah, that's sort of -- by definition, cancer has already evaded apoptosis.
Q. Exactly.
Cancer also needs to develop sustained angiogenesis; correct?
A. It needs to derive a blood supply, and angiogenesis is the blood supply.
Q. It needs the ability to invade other tissue and metastasize; correct?
MS. O'DELL: Object to the form.
THE WITNESS: I'm not sure it needs to. I mean, in general, the time course is one of invasion

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or metastasis or both.
BY MS. BOCKUS:
Q. Okay. Which of those steps do you believe talc contributes to?
MS. O'DELL: Objection to form.
THE WITNESS: I believe talc contributes to the first onset -- or the additional or first onset of mutations that then lead on to cancer.
BY MS. BOCKUS:
Q. What -- in what gene does the mutation occur in that talc impacts?
MS. O'DELL: Object to the form.
THE WITNESS: Some genes -- SNPs that Dr. Saed has identified are what we know, I think, to date. We know there's other genetic mutations that are present in the somatic form of ovarian cancer as well as the inherited genes.
But I don't think anybody has studied that in correlation with talc exposure, so that would be an interesting investigation to undertake.
BY MS. BOCKUS:
Q. Inflammation -- chronic inflammation, is that associated with pain?
A. With pain?
Q. Yes.

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A. It might be.
Q. Is chronic inflammation associated -- well, let me back up.
You testified earlier that you would not expect to see signs of chronic inflammation at the time you operate on a woman with ovarian cancer; is that correct?
MS. O'DELL: Object to the form.
THE WITNESS: Yes, that's true.
BY MS. BOCKUS:
Q. Why would you no longer see the signs of chronic inflammation at the time of her surgery for ovarian cancer?
A. One, I'm not sure we know the signs that a surgeon would identify as chronic inflammation to my naked eye or to my field.
Two, most of the time in women with ovarian cancer, three-quarters of the women I take care of have cancer spread throughout their abdomen and pelvis, with cancer everywhere, so that -- I mean, we don't -- I don't know how to identify chronic inflammation. I suggested that ascites has something to do with inflammation but not always.
Q. And the ascites could come from the cancer itself; correct?

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A. Yes.
Q. What would signs of chronic inflammation in the fallopian tubes be?
MS. O'DELL: Object to the form.
THE WITNESS: I don't think there's any signs that I'm aware of that recognize -- or would be identified as chronic inflammation.
BY MS. BOCKUS:
Q. Is chronic inflammation something that could be identified by a pathologist?
A. It might be.
Q. Do you know whether there have been any studies looking at -- looking for signs of chronic inflammation in women whose fallopian tubes have been removed as part of any of the studies that you cite?
MS. O'DELL: Object to the form.
THE WITNESS: I'm sorry. They've had their fallopian tubes removed?
BY MS. BOCKUS:
Q. And looked at by a pathologist, yes. And it's reported in the studies.
A. Signs of chronic inflammation of the fallopian tube? I'm not aware of that, no.
Q. Okay. Would you expect a woman who is using talcum powder regularly to have signs of inflammation

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in her fallopian tubes?
MS. O'DELL: Objection. Form.
THE WITNESS: Again, the signs of chronic inflammation are vague and not well defined in terms of what a pathologist would see. If they did molecular testing -- for example, the reason we now believe that most ovarian cancers arise in the fallopian tube is by doing molecular testing of the fallopian tube and seeing p53 mutations and early cancers arising from the fallopian tube that then metastasize to the ovary in the peritoneal cavity. So that's a molecular biology approach that pathologists don't usually do unless it's in a research setting.
BY MS. BOCKUS:
Q. Is it your belief that pathologists cannot identify chronic inflammation in tissue samples that they examine?
MS. O'DELL: Objection. Form.
THE WITNESS: I think they can identify it on some occasions on H&E slides. Is that what you're talking about?
BY MS. BOCKUS:
Q. Yes.
A. I think they can see it sometimes.
Q. And do you know if chronic inflammation is

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reported as existing in the fallopian tubes in any of the studies that you have cited in your report?
MS. O'DELL: Objection. Asked and answered.
THE WITNESS: Not that I'm aware of, no.
BY MS. BOCKUS:
Q. I'm going to be jumping around a lot, and I'm just going to apologize in advance for that --
A. Okay.
Q. -- but so much of what I was going to ask you has already been covered.
Did I understand you correctly to say that it is your belief that age causes ovarian cancer?
A. Age causes ovarian cancer?
Q. Yes.
A. Age allows time for mutations to occur; and, therefore, ovarian cancer comes from that.
Q. Do you know what the relative risk of ovarian cancer is for a woman in her 60s compared to a woman in her 30s?
A. I'd have to look at some statistical tables. I'm sure it's available.
Q. But it's greater than three or four; correct?
MS. O'DELL: Object to the form.

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THE WITNESS: I'm not sure how much greater. It's greater as women age.
BY MS. BOCKUS:
Q. You indicated that not using birth control pills causes ovarian cancer.
Did I understand you correctly?
MS. O'DELL: Object to the form.
THE WITNESS: It allows, more likely than not, more mutations to occur as the patient ovulates rather than having ovulation suppression by birth control pills.
BY MS. BOCKUS:
Q. Okay. Do you believe that that mechanism is supported in light of the fact that it is now believed that cancers originate in the fallopian tubes?
A. Yes, I think it's hormonal changes in the fallopian tubes as well as the ovary.
Q. Okay. Do you know to what -- what are the odds ratios for a woman developing ovarian cancer who has never used birth control pills compared to women who have?
A. There's one statistic, I think, that is pretty well agreed upon is that women who used birth control pills for five years have about a 50 percent reduction in the lifetime risk of ovarian cancer.

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Q. In your report on page 4, at the bottom, you talk about EOC risk factors.
Can you see where I'm talking about?
A. Yes, ma'am.
Q. And you say (as read):
"The lifetime risk of developing ovarian cancer is 39 to 46 percent in BRCA1 carriers."
Did I read that correctly?
A. Yes.
Q. So does that come out to 390 to 460 women per thousand who carry the BRCA1 gene mutation will develop ovarian cancer in their lifetime?
MS. O'DELL: Objection to form.
THE WITNESS: Give me a second to do the math. So if we had a thousand women, in their lifetime, 390 would develop ovarian cancer.
BY MS. BOCKUS:
Q. Okay. Somewhere between 390 and 460?
A. Yes. I just did the math for one, but yes.
Q. Okay. And then going on, women who carry the BRCA2 mutation, it would be 110 to 270 out of 1,000 in their lifetime would develop ovarian cancer; is that correct?
A. Yes.

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MS. O'DELL: For women with BRCA2?
MS. BOCKUS: Yes. For women with BRCA2. I thought I made that qualification.
BY MS. BOCKUS:
Q. And then you say (as read):
"This is compared to the 1.3 percent lifetime risk in noncarriers."
Correct?
A. That's correct.
Q. So in other words, 13 women out of 1,000, approximately, in the US will develop ovarian cancer in their lifetime?
MS. O'DELL: Objection to form.
BY MS. BOCKUS:
Q. Is that what that means?
A. Yes.
MS. O'DELL: Objection to form.
BY MS. BOCKUS:
Q. And it's your opinion that -- and that's all-comers; right? That's women who have had children, women who haven't had children, et cetera?
A. Yes.
Q. That's the entire population?
A. But that don't have these BRCA mutations.

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Q. Correct. Fair enough.
So, as I understand it, it is your opinion that the use of body powders, talcum body powders, increases a woman's risk by about 30 percent. Is that correct?
A. That's what the epidemiology says, yes.
Q. Okay. So does that mean that, instead of 13 out of 1,000 women who use talcum powder, then you would expect to see 17 out of 1,000 who would develop ovarian cancer in their lifetime?
MS. O'DELL: Object to the form.
THE WITNESS: I'd have to do the math, but that sounds about right.
BY MS. BOCKUS:
Q. And out of those 17 per thousand, 13 would have developed it anyway; correct?
MS. O'DELL: Object to the form.
THE WITNESS: Yes.
BY MS. BOCKUS:
Q. And do you know of any methodology that would allow you to identify which of the 4 out of 17 developed ovarian cancer because of their use of talc as opposed to just being on this planet and living a certain number of years?
MS. O'DELL: Object to the form.

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THE WITNESS: Being on the planet is the 1.3 percent, or the 13 out of 1,000.
BY MS. BOCKUS:
Q. Correct.
A. Being exposed to talc adds the other 4, if your math is right --
Q. Okay. But do you know of any way that you or anyone else can say, in this group of 17 women who have ovarian cancer who used talcum powder, it's these 4 who developed it because of their talcum powder use versus the 13 that we know would have been diagnosed with ovarian cancer whether they ever used talc or not?
MS. O'DELL: Objection. Incomplete hypothetical.
THE WITNESS: So this is a hypothetical that 1,000 women used talcum powder, and we knew, if they hadn't used talcum powder, that 1 point -- that 13 of them would develop it, and then the other 4 develop it because, in my opinion, they used talcum powder?
BY MS. BOCKUS:
Q. Right, because that's the difference between the background rate and the rate that, it's your opinion, is associated with talc use; correct?

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A. So do I know which one of those -- what number are we up to now?
Q. The 4 out of 17.
A. -- the 4 out of 17 --
Q. Yes.
A. -- was caused by talcum powder?
Q. Right.
A. I don't think I can say that.
Q. Do you know of any methodology that would allow someone to identify which of the 4 out of 17 were associated with their talc use versus associated with just living that long?
MS. O'DELL: Objection to form.
THE WITNESS: I'm not aware of any -- if you're talking about biomarkers or something else, I'm not aware of any that would distinguish between cancer caused by talc and cancer caused by age alone.
BY MS. BOCKUS:
Q. Okay. And if one were to guess, they would be mistaken two times out of three; correct?
MS. O'DELL: Object to the form.
THE WITNESS: To guess about what?
BY MS. BOCKUS:
Q. Which of the 17 had ovarian cancer because of their talc use as opposed to because they would have

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gotten it anyway?
MS. O'DELL: Object to the form.
THE WITNESS: I'm not quite sure I understand where you're going or what the question is. I think the answer is we don't -- we won't -- we can't identify which one of those patients that have ovarian cancer because they all -- your hypothetical is that they all were exposed to talc.
MS. O'DELL: I don't think that was her hypothetical.
THE WITNESS: Okay. Well, then I've lost this.
BY MS. BOCKUS:
Q. As I under -- well, let me just move on.
When women go swimming in a swimming pool, does chlorinated water go into their uterus?
A. Goes into their vagina.
Q. That wasn't my question. Does it go to their uterus?
A. Probably not.
Q. Why not?
A. I don't know the answer to that question.
Q. When women go swimming in the ocean, does saltwater go into their uterus?
A. Not usually, no.

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Q. Why not?
A. It just doesn't.
Q. Is there something blocking the uterus from the vagina?
A. The cervix is there, and there is mucus in the cervix at certain times. I think the other, to follow up on your question with a little bit better answer, is that exposure to the water is limited. It's not like the patient's in the water for hours, day after day after day.
Q. That really wasn't my question.
A. Okay.
Q. My question has to do with the passage of any kind of particles from outside the human body to inside the human body -- the female body.
A. Okay.
Q. Is it your opinion that particles contained in bathwater make their way into the fallopian tubes?
A. I don't have an answer -- answer or opinion on that.
Q. Same question for swimming pool water.
A. Likewise.
MS. O'DELL: Objection to form.
BY MS. BOCKUS:
Q. Do you know whether there's an increased

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incidence of ovarian cancer in women who have been competitive swimmers?
A. Not that I'm aware of.
Q. Those women clearly will have spent hours a day, every day, in a swimming pool for many years of their life; correct?
A. Yes.
Q. And you would expect, would you not, if particles from outside a woman's body could freely move into the inside of her body, that the chlorine and other particles found in a swimming pool would make their way to their ovaries; correct?
A. They could. But if they're not carcinogens, then they wouldn't cause any problem.
Q. Would any foreign body that makes its way to its ovary -- to a woman's ovary cause a foreign body reaction?
A. Not necessarily.
Q. What foreign particle could make its way to a woman's ovary and not cause a foreign body reaction?
MS. O'DELL: Objection to the form.
THE WITNESS: I think that those that don't cause inflammation, those that are not cleared. We talked about cornstarch earlier in today's proceedings, and cornstarch seems not to cause an

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inflammatory reaction. It gets cleared by the immune system, and it dissolves.
BY MS. BOCKUS:
Q. Does cornstarch make it to the ovary?
A. Cornstarch has been documented to get to the ovary, yes.
Q. Has it been associated with foreign body reaction in the ovary?
A. Not that I'm aware of.
Q. Do you know whether pelvic mesh causes ovarian cancer?
A. Mesh?
Q. Yes.
A. Not that I'm aware of.
Q. Is pelvic mesh a foreign body?
A. Yes. It's in the vagina or -- yeah, it's placed in the vagina, not in the peritoneal cavity per se.
Q. Does pelvic mesh cause chronic inflammation?
A. Not that I'm aware of. I think it causes acute inflammation and an ingrowth of fibroblasts and fibrous tissue to cause -- to get the result that the surgeon wants and the patient wants.
Q. Just because something is classified as a carcinogen doesn't mean it's carcinogenic to every

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organ in the body; correct?
A. I think that's fair to say.
Q. And I think you told us previously that, to your knowledge, you're not aware of nickel, chromium, or cobalt ever being identified as carcinogenic to the ovary; correct?
A. I'm not aware that anybody's ever tested that hypothesis.
Q. Did you look at the IARC classifications of those three heavy metals?
A. Yes.
Q. And did you see where IARC did not identify that they were carcinogenic to the ovary?
MS. O'DELL: Objection to form.
THE WITNESS: Right. I'm not sure that there's any data, going back to my answer to my last question, where that's ever been tested. So two of those heavy metals are considered carcinogens, but not specifically to the ovary because they haven't been tested in the ovary.
BY MS. BOCKUS:
Q. So without that -- without those tests, you can't say one way or the other whether those heavy metals, the three you identify in your report, increase the risk of ovarian cancer, can you?

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MS. O'DELL: Object to the form.
THE WITNESS: I think they're contained within Johnson's baby powder.
BY MS. BOCKUS:
Q. That wasn't my question.
Without science to support that, you cannot say that these three heavy metals that you identify in your report cause or contribute to cause ovarian cancer; correct?
MS. O'DELL: Object to the form.
THE WITNESS: I think they're in Johnson baby powder and the baby powder causes ovarian cancer. So something amongst that, including the heavy metals, is contributing to the onset of ovarian cancer.
BY MS. BOCKUS:
Q. And you're comfortable saying that without any science to support it; correct?
MS. O'DELL: Objection to form.
THE WITNESS: The science is the epidemiology of increased risk of ovarian cancer in women that are exposed to Johnson baby powder.
BY MS. BOCKUS:
Q. Did I understand your testimony previously that it is your opinion that the Women's Health

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Initiative is a poorly designed, poorly executed study?
MS. O'DELL: Object to the form.
THE WITNESS: Yes.
BY MS. BOCKUS:
Q. Is it your opinion that the Nurses' Health Study is a poorly designed, poorly executed study?
MS. O'DELL: Object to the form.
THE WITNESS: With regard to the detection of ovarian cancer being caused by perineal use of talcum powder, yes.
BY MS. BOCKUS:
Q. Is it your opinion that the Gonzalez Sister Study is a poorly designed, poorly executed study?
A. Yeah. That's the worst one.
Q. You have testified -- and this certainly would be part of your practice to understand -- that we now know that HPV causes cervical cancer; correct?
A. That's correct.
Q. What is the odds ratio of developing cervical cancer in women who have HPV -- or who have had HPV versus those who have not?
A. HPV is nearly 100 percent -- let me turn this back around.
Women with squamous cell carcinoma of the

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cervix, which is the most common type, almost all -- as close to 100 percent as possible -- have been infected with HPV.
Q. And that allows the scientific and medical community to conclude with consensus that HPV causes cervical cancer; correct?
A. Yes, but not in all women that are infected with HPV.
Q. There is no similar factor for ovarian cancer as closely linked as HPV is to cervical cancer, is there?
MS. O'DELL: Objection to form.
THE WITNESS: I'm not sure I understand the question.
BY MS. BOCKUS:
Q. Because it wasn't a very good one.
A. Okay.
Q. You indicated that close to 100 percent of all women who develop a specific -- the most common type of cervical cancer have had HPV; correct?
A. That's correct.
Q. There is nothing even close to that in terms of an exposure and ovarian cancer; correct?
A. Yes, I would agree.
Q. Do you know what percentage of sperm make it

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to the fallopian tube from a single ejaculation?
A. I don't.
Q. You know that that's been studied; correct?
A. I don't know that. The last time I did any reproductive endocrinology was in 1975. So I don't know what's --
Q. Let me ask you --
A. -- been studied.
Q. I apologize. I didn't mean to interrupt.
A. Yes.
Q. Do you have any reason to believe that a talc particle would fare better than a sperm in terms of its chances of making it from the vagina to the ovary?
MS. O'DELL: Object to the form.
THE WITNESS: No.
BY MS. BOCKUS:
Q. Do you think that it's probably that fewer talc particles -- or a smaller percentage of talc particles deposited into the vagina would make it to the ovary than percentage of sperm?
A. I don't have an opinion.
Q. Okay. With regard to studies by Dr. Saed, do you believe that it would have been appropriate for Dr. Saed to indicate on those studies that his research was being funded by plaintiffs' lawyers in

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this litigation?
MS. O'DELL: Object to the form.
THE WITNESS: I'm not sure I understand exactly what was his funding.
BY MS. BOCKUS:
Q. For the studies that you're relying on, the Saed studies that you have relied on in your report.
A. I'm not aware of the extent of the funding, if it was from the attorneys -- the plaintiffs' attorneys.
Q. Assuming that the evidence will show that the funding for Dr. Saed's experiments came from plaintiffs' attorneys, would it be appropriate and ethical for a physician to reveal that that's the source of their funding?
MS. O'DELL: Objection to form.
THE WITNESS: So peer-reviewed journals have certain conflict of interest statements and disclosures that are asked as part of the peer review process of accepting a manuscript. So I'm not sure what the policies are of this particular journal.
BY MS. BOCKUS:
Q. So does such a conflict of interest only have to be revealed if it's the policy of the journal?
MS. O'DELL: Objection to form.

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THE WITNESS: I think the journal, if it's going to publish, would want to make sure that they are publishing information that's correct and, you know, through the peer review process, and also any conflicts of interest are declared, any sources of funding are usually declared, including grants from National Institutes of Health, for example.
BY MS. BOCKUS:
Q. When Dr. Saed placed talc on these cultured ovarian cancer cells, one of the findings that he reported was that it increased the level of CA-125; correct?
A. Yes.
Q. You would agree that CA-125 is raised by many things; correct?
A. Yes, including inflammation -- in particular inflammation in terms of a false positive CA-125.
Q. It can be raised by pregnancy; is that right?
A. Yes.
Q. Can be raised by cirrhosis of the liver?
A. Yes.
Q. Can be raised by uterine fibroids; correct?
A. Yeah --
Q. By all kinds of things?
A. -- among other things, yes.

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Q. And Dr. Saed did not use any positive or negative controls in his study, did he?
MS. O'DELL: Objection. Form.
THE WITNESS: He did use controls in his study.
BY MS. BOCKUS:
Q. Did Dr. Saed use any controls in which he applied a -- something like glass beads to the same tissue to see what the reaction would be compared to the talc he was applying?
MS. O'DELL: Objection to form.
THE WITNESS: So applying glass -- I'm not a laboratory scientist, but putting glass beads into a culture plate, for example? So that would be potentially another inflammatory product, so I don't know why one would put glass beads into the control plate.
He has controls in all of his tables here (indicating). It's just the medium that the talc is suspended in. So the medium didn't cause the changes that he demonstrates in these cancer cells and these epithelial cells. It was the talc that caused the changes. That's why you do a control.
BY MS. BOCKUS:
Q. But a -- but to do a control with regard

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to -- to determine whether talc causes these cells to react differently than other items that have previously been shown not to cause inflammation in the cells, you would need to add something in addition to the medium; correct?

MS. O'DELL: Objection to form.

THE WITNESS: No. That's what a control is. Why would you add anything? That would be a third experiment. You've got your controls and now your glass beads and now your talc.

BY MS. BOCKUS:

Q. Is it your understanding that glass beads would cause inflammation to the ovarian epithelial?

A. I don't know what they do. I don't know why one would put glass beads in a control.

Q. Other than the medium, did Dr. Saed include -- did he do any test to determine whether other particulate would cause the exact same reaction as the talc?

A. I don't think that was part of his experimental design.

Q. Do you think that would have been an appropriate experimental design to determine if talc elicited a response different than any other foreign particulate?

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MS. O'DELL: Object to the form.

THE WITNESS: Oh, you could do an extensive experiment of all kinds of particulates and compare it with talc. That wasn't the question he was trying to ask. I'm not quite sure where you're going with this. I mean...

BY MS. BOCKUS:

Q. To determine whether the changes that he noted actually cause cancer would take more steps; correct?

A. Yes. He's showing --

MS. O'DELL: Object to the form.

THE WITNESS: -- that there's gene mutations. They are the first step -- or the next step towards cancer.

BY MS. BOCKUS:

Q. And all of our -- we all have gene mutations going on in our bodies every day; correct?

A. Yes. A little scary.

Q. And we all have -- thank God, the way we're put together, there are systems in place that detect gene mutations and kill them; correct?

A. Apoptosis. Yes.

Q. And so the fact that a gene mutation is caused in a Petri dish is a long ways from proving

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that that particulate -- in this case, talc -- causes cancer; correct?

MS. O'DELL: Object to the form.

THE WITNESS: It doesn't -- it's not conclusive, but it certainly is a step in the process leading towards cancer.

BY MS. BOCKUS:

Q. And there are specific tests that can be done for genotoxicity; correct?

Are you familiar with those --

A. I'm not familiar with what that exactly means.

Q. Have you seen studies where, in the lab, they have started this process, such as Dr. Saed did with causing a single gene mutation, and then implanting that tissue into a lab animal to see if it actually grows into a cancer?

MS. O'DELL: Object to the form.

THE WITNESS: I'm not aware of that, but it's certainly -- I presume it's possible to do something like that, but I'm not sure.

BY MS. BOCKUS:

Q. I think you've answered this question. And if you have, I apologize.

What is the threshold response for talc?

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MS. O'DELL: Object to the form.

THE WITNESS: The threshold response that would induce cancer, I presume is what you're really asking?

BY MS. BOCKUS:

Q. Yes, sir. Thank you.

A. I don't think we know that.

MS. BOCKUS: That's all that I have. Thank you.

THE WITNESS: Thank you.

MS. BOCKUS: I'll cede back my last 15 minutes to the other defense counsel who are here.

MS. O'DELL: Do you have questions?

MR. BILLINGS-KANG: I don't think so, no.

MS. O'DELL: Do you have questions?

MR. ZELLERS: No further questions.

MR. MIZGALA: I want to ask a question.

MR. ZELLERS: Please do.

CROSS-EXAMINATION BY COUNSEL FOR THE DEFENDANT PTI

BY MR. MIZGALA:

Q. Doctor, on page 2 of your report, at the bottom --

A. Yes.

Q. -- you write (as read):

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"I approached each article objectively and critically, assessing for factors such as design, power, reputation of the authors, quality of the journal, and potential biases."

Correct?

A. Yes, that's what I wrote.

Q. Where is that -- where is that written down? Where is it compiled?

A. Where is what compiled?

Q. All those things that you assessed? Did you reduce that to writing anywhere?

A. No. I mean, these are the articles I identified and reviewed and assessed (indicating).

Q. Okay. So you don't have a spreadsheet or something of all these factors that you assessed?

A. No.

MS. O'DELL: Objection to form.

THE WITNESS: No.

BY MR. MIZGALA:

Q. In your head?

A. In my head at the time, and I chose articles that I thought were appropriate to put into my report.

MR. MIZGALA: Okay. No further

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questions.

MS. O'DELL: Let's go off the record.

THE VIDEOGRAPHER: Going off record at 5:23 p.m.

(Recess taken from 5:23 p.m. to 5:40 p.m.)

THE VIDEOGRAPHER: Back on the record at 5:40 p.m.

CROSS-EXAMINATION BY COUNSEL FOR THE PLAINTIFFS

BY MS. O'DELL:

Q. Dr. Clarke-Pearson, I have just a few questions to ask you.

First, let me ask you, in regard to asbestos, can asbestos be inhaled and cause ovarian cancer?

MR. ZELLERS: Objection to form.

THE WITNESS: Yes.

Yes. IARC has deemed that true, to be the case that it can cause ovarian cancer by inhalation.

BY MS. O'DELL:

Q. And, similarly, can fibrous talc be inhaled and cause ovarian cancer?

MR. ZELLERS: Objection. Form.

THE WITNESS: Yes. The same answer.

BY MS. O'DELL:

Q. You were asked a series of questions about --

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and they were hypotheticals, as I recall -- regarding specific patients and the cause or causes of their ovarian cancer.

In regard to a woman who has potentially, say, a BRCA mutation -- maybe she's of a certain age -- and she's a routine user of talcum powder such as Johnson's baby powder, do you have an opinion as to what the causes of her cancer would be?

MR. ZELLERS: Objection. Form.

THE WITNESS: So several causes, but the talcum powder would have to be considered a contributing cause to her ovarian cancer.

BY MS. O'DELL:

Q. For a woman who has -- in whom there's not been identified a known risk factor but she is a routine user of talcum powder such as baby powder or Shower to Shower, do you have an opinion as to what one of the causes of her cancer -- ovarian cancer would be?

MR. ZELLERS: Objection. Form.

THE WITNESS: What I've been trying to say all day is the Johnson & Johnson baby powder causes ovarian cancer. In this particular patient, it is a significant contributing cause.

MS. O'DELL: I have nothing further,

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Doctor. Thank you.

THE WITNESS: Okay. Thank you.

FURTHER EXAMINATION BY COUNSEL FOR THE JOHNSON & JOHNSON DEFENDANTS

BY MR. ZELLERS:

Q. The asbestos studies that you referred to earlier dealing with inhalation, those were occupational studies; correct?

MS. O'DELL: Object to the form.

THE WITNESS: Yes.

MR. ZELLERS: Okay. I have no further questions.

MS. BOCKUS: I have one.

FURTHER EXAMINATION BY COUNSEL FOR THE DEFENDANT IMERYS

BY MS. BOCKUS:

Q. Doctor, are you aware of any study that indicates that women who carry a BRCA gene mutation and uses -- and has a lifetime history of using talcum powder is at a higher risk of developing ovarian cancer than women who have the BRCA gene mutation and have never used talcum powder?

MS. O'DELL: Objection to form.

THE WITNESS: It would be my opinion that talcum powder would increase the patient's chance

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of having ovarian cancer. I'm not aware of any study that's been able to investigate that to date.
BY MS. BOCKUS:
Q. That is something that could be investigated; correct?
MS. O'DELL: Object to the form.
THE WITNESS: In a case-control study, yes.
BY MS. BOCKUS:
Q. But to your knowledge, it's never been reported; correct?
A. Not that I'm aware of.
MS. BOCKUS: That's all I have.
THE WITNESS: Thank you, everybody.
MR. ZELLERS: Thank you, Doctor.
THE VIDEOGRAPHER: Just one second.
This concludes the deposition of Dr. Daniel Clarke-Pearson. Time going off the record is 5:44 p.m.
(Whereupon, at 5:44 p.m., the deposition ceased.
Signature was reserved.)

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ACKNOWLEDGMENT OF DEPONENT

I, DANIEL L. CLARKE-PEARSON, M.D., do hereby acknowledge that I have read and examined the foregoing testimony, and the same is a true, correct, and complete transcription of the testimony given by me, and any corrections appear on the attached errata sheet signed by me.

_________________ ______________________

(DATE) (SIGNATURE)

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E R R A T A

CASE NAME: TALCUM POWDER LITIGATION MDL NO. 2738CASE
WITNESS NAME: DANIEL L. CLARKE-PEARSON, M.D.
CASE NUMBER: 16-2738 (FLW)(LHG)

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STATE OF NORTH CAROLINA)
) C E R T I F I C A T E
COUNTY OF ORANGE)

I, Sophie Brock, Court Reporter and Notary Public, the officer before whom the foregoing proceeding was conducted, do hereby certify that the witness(es) whose testimony appears in the foregoing proceeding were duly sworn by me; that the testimony of said witness(es) were taken by me to the best of my ability and thereafter transcribed under my supervision; and that the foregoing pages, inclusive, constitute a true and accurate transcription of the testimony of the witness(es).

I do further certify that I am neither counsel for, related to, nor employed by any of the parties to this action, and further, that I am not a relative or employee of any attorney or counsel employed by the parties thereof, nor financially or otherwise interested in the outcome of said action.

This, the 6th day of February, 2019.

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Sophie Brock, RPR, RMR, RDR, CRR
Notary Number: 200834000001

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Vineis *et al. Emerg Themes Epidemiol (2017) 14:7*
DOI 10.1186/s12982-017-0061-7

Emerging Themes in Epidemiology

COMMENTARY Open Access

Causality in cancer research: a journey through models in molecular epidemiology and their philosophical interpretation

Paolo Vineis[1*†], Phyllis Illari[2†] and Federica Russo[3†]

Abstract

In the last decades, Systems Biology (including cancer research) has been driven by technology, statistical modelling and bioinformatics. In this paper we try to bring biological and philosophical thinking back. We thus aim at making different traditions of thought compatible: (a) causality in epidemiology and in philosophical theorizing—notably, the "sufficient-component-cause framework" and the "mark transmission" approach; (b) new acquisitions about disease pathogenesis, e.g. the "branched model" in cancer, and the role of biomarkers in this process; (c) the burgeoning of omics research, with a large number of "signals" and of associations that need to be interpreted. In the paper we summarize first the current views on carcinogenesis, and then explore the relevance of current philosophical interpretations of "cancer causes". We try to offer a unifying framework to incorporate biomarkers and omic data into causal models, referring to a position called "evidential pluralism". According to this view, causal reasoning is based on both "evidence of difference-making" (e.g. associations) and on "evidence of underlying biological mechanisms". We conceptualize the way scientists detect and trace signals in terms of *information transmission*, which is a generalization of the mark transmission theory developed by philosopher Wesley Salmon. Our approach is capable of helping us conceptualize how heterogeneous factors such as micro and macro-biological and psycho-social—are causally linked. This is important not only to understand cancer etiology, but also to design public health policies that target the right *causal* factors at the macro-level.

Keywords: Systems biology, Evidential pluralism, Information transmission, Difference-making, Mechanism

Introduction

What we mean by "cause of a disease" has an obvious practical significance, for example for the development of drugs and preventive interventions (e.g. vaccination programmes). We believe that—building on current models of cancer causality, and in particular the model offered by "molecular epidemiology" [1]—there is the need to reconcile the conceptual interpretation of causality and its biological foundation. In this paper we address the meaning of causality in the case of cancer. For many cancers, causes are still elusive and there is confusion in the literature between cause and mechanism. Mechanisms do not need to be fully known for hazard identification (which can come from epidemiology alone, as was the case of smoking and cancer), but knowledge of mechanisms supports causal reasoning in both hazard identification and risk assessment (this is the idea of "evidential pluralism" that we also discuss later).

In addition to the practical implications, there are also important conceptual (philosophical) aspects in defining what a cause is, with cancer being an interesting case. This is particularly pressing, in the light of the advancements of molecular biology and the use of biomarkers in cancer research.

We first summarize the current views on carcinogenesis, and then explore the relevance of current philosophical interpretations of causality. We argue that using

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mechanisms to support causality claims in observational epidemiology is not just a matter of adding more fine-grained associations, but to understand "why" there are such associations. Our proposal is that the identification of causes of cancer rests on two components: (1) "difference-making", and (2) "mechanism". For example, in the recent controversy on the carcinogenicity of red meat [2], the epidemiological literature consistently detected an increase in risk of colon cancer among red meat eaters (difference-making), but further confirmation of a causal relationship came from the mechanisms involved, such as the formation of carcinogenic nitroso-compounds in the intestine of red meat eaters. Risk is just a measure of how much individual probability of cancer increases (e.g. in the exposed compared to the unexposed), conditionally on red meat consumption, but—with notable exceptions—a sound conclusion for a causal relationship also requires the identification of a plausible mechanism [3].

The molecular basis of cancer: the microenvironment underlying macroenvironmental causes

We start with the mechanisms that underlie cancer onset, i.e. the sequence of molecular events that lead from a normal cell to a cancer cell. This is necessary to understand causality, in the framework of cancer as an evolutionary (Darwinian) process. It is important to stress that cancer is not a single entity, and therefore pathways leading to cancer onset are diversified. There have been several important developments in the molecular interpretation of carcinogenesis in recent decades, including (a) a wide set of mutagenic events which encompasses single base substitutions as well as larger structural genetic alterations; (b) an understanding of the crucial role of epigenetic changes (defined as functional changes in DNA that do not involve a change in the nucleotide sequence); (c) an acknowledgement of the importance of selection of mutated or epimutated cells; and (d) the unifying concept of "branched evolution", i.e. evolution occurs in a branched manner in several tumor types, leading to intratumor diversity, with the selective advantage of any genotype depending on the environment [4].

There are several implications for primary prevention derived from this definition (represented in Additional file 1: Figure S1).

- Cancers occur in stages that correspond to increasing complexity of molecular changes ("intratumor diversity"), with two metastases or two areas in the same localized tumour having a different set of mutations.
- Mutations can be neutral, detrimental or favorable for the expansion of a cell clone, depending both on the micro-environment, that exerts a selective pressure, and the previous history of mutations in the same cell. The latter concept is called "historical contingency" [5] and corresponds to the influence that previous mutations have on the effects of subsequent mutations on protein structure and function, and also on the evolution of entire gene regulatory networks [5].
- In the onset of cancer in individuals, both mutagens and "selectogens" play a role, i.e. the individual cancer reflects the history of exposures that both induce mutations and facilitate the selection of existing mutations. Selectogens may include known risk factors for cancer, such as the metabolic syndrome, that are unlikely to have a mutational mechanism as their main mode of action, and may predominantly act by promoting the selection of cells already carrying somatic mutations.

Smith et al. [6] have identified ten "hallmarks of carcinogens", in the context of the IARC Monographs (Table 1); these correspond to the main mechanisms identified so far in the pathways to cancer, and at least four of these are not based on mutagenesis, e.g. chronic inflammation.

Table 1 Key characteristics of carcinogens (from Smith et al. [6])

1. Is electrophilic or can be metabolically activated
Parent compound or metabolite with an electrophilic structure (e.g. epoxide, quinone, etc.), formation of DNA and protein adducts
2. Is genotoxic
DNA damage (DNA strand breaks, DNA protein cross-links, unscheduled DNA synthesis), intercalation, gene mutations, cytogenetic changes (e.g. chromosome aberrations, micronuclei)
3. Alters DNA repair or causes genomic instability
Alterations of DNA replication or repair (e.g. topoisomerase II, base-excision or double-strand break repair)
4. Induces epigenetic alterations
DNA methylation, histone modification, microRNA expression
5. Induces oxidative stress
Oxygen radicals, oxidative stress, oxidative damage to macromolecules (e.g. DNA, lipids)
6. Induces chronic inflammation
Elevated white blood cells, myeloperoxidase activity, altered cytokine and/or chemokine production
7. Is immunosuppressive
Decreased immunosurveillance, immune system dysfunction
8. Modulates receptor-mediated effects
Receptor in/activation (e.g. ER, PPAR, AhR) or modulation of exogenous ligands (including hormones)
9. Causes immortalization
Inhibition of senescence, cell transformation
10. Alters cell proliferation, cell death or nutrient supply
Increased proliferation, decreased apoptosis, changes in growth factors, energetics and signaling pathways related to cellular replication or cell cycle

It is likely that in the "branched evolution" paradigm, risk factors acting via these mechanisms play the role of selectogens. It will also be critically important to understand how such non-mutagenic environmental exposures may interact with cellular processes that maintain the fidelity of DNA (e.g. DNA repair and replication), thus affecting the "endogenous" mutations seen in different types of human tumours.

Macroenvironmental causes of cancer

How are these concepts, at the level of the micro-environment, connected to external exposures in the macro-environment? Based on epidemiological evidence, we know that some 40–50% of cancers would be preventable if current knowledge about risk factors were to be translated into preventive interventions [7–9]. There is broad consensus on these estimates in the epidemiological community, though the concept of "attributable risk" is still debated and is methodologically weak (for limitations see [10]).

These preventable cancers are for the most part explained by external (or internal—such as endogenous nitrosation) exposures that are unlikely to act in isolation: even a "necessary" cause of cancer, human papilloma virus (HPV), is itself not sufficient to cause cervical cancer in an individual. Though all cervical cancers need exposure to HPV, being exposed to HPV needs other additional components in the causal constellation that led to an individual's cancer. On a population scale, HPV is probably able to explain 100% of cervical cancer cases (in principle cervical cancer can be eradicated by vaccination), but each individual case is not entirely explained by HPV alone: for example, exposure to the virus happens in a socio-economic context that is also part of the etiology of cancer (including other sexually-transmitted infections and behaviours that interact with the virus).

The model of causation that applies to single individuals is called the "sufficient-component-cause framework", and it considers sets of actions, events, or states of nature that together lead to the outcome under consideration. This concept has been popularized by Rothman et al. [11] through the metaphor of "pies": the constellation of exposures that has led to cancer in an individual or a group of individuals is represented as a pie where the slices are different components and the totality of them is causally sufficient. The model gives an account of the multiple causes that in their combination lead to a particular effect. The model usefully captures multi-causality and the interaction between component causes (in other words their "organization").

The above concepts allow us to bring together two domains that have been separated so far: the "ecology of cancer" at a population level (the macro-environment) and the mechanisms of carcinogenesis (the micro-environment) at the individual level. Additional file 2: Figure S2 shows the "ecology" of some common cancers in different countries, though the picture is rapidly changing because of globalization [12]: the Figure suggests that in each area there are some forms of cancer that prevail due to the local predominant exposures. Such exposures are likely to be a mixture of mutagens, such as aflatoxin B1, and selectogens, such as chronic inflammation caused by the hepatitis B virus; these two factors combine to increase the risk of e.g. hepatocellular carcinoma in Asia and sub-Saharan Africa. In other cases a single complex mixture, e.g. tobacco smoke, can comprise a combination of mutagens and selectogens.

The future challenge will be to monitor this complex and changing ecology of cancer (and other non-communicable diseases), and to relate these changes and interpret their effects with respect to the micro-environmental modifications. Equally, starting with the molecular modifications observed at the level of the micro-environment can reveal clues as to the ecology of cancer at the macro-environmental level. An example comes from the recent observation that renal cell cancers in some regions in Europe have a somatic mutation spectrum that reflects exposure to an environmental carcinogen, aristolochic acid, previously considered as a risk factor for upper urothelial tract cancers [13].

The attempt to connect the external (macro) with the internal (micro) environment has been explored within "exposome" research [14]. While the macro-environment represents the "external exposome", the micro-environment can be explored as a part of the "internal exposome" using the new high-throughput technologies of epigenomics, transcriptomics, miRNA, proteomics and metabolomics. The connection between the external environment and internal biological changes has been the goal of molecular epidemiology for decades, as expressed for example in Schulte and Perera's [1] book. New technologies can in principle allow us to monitor how the micro-environment can lead to selection of mutations and thus identify selectogens as additional targets for prevention. There are great expectations towards these omic technologies for the development and validation of a suite of new biomarkers to monitor the micro-environmental changes underlying cancer development.

It is becoming increasingly clear that non-communicable diseases are influenced by events that took place throughout an individual's life-course, in both the macro- and micro-environments. The concept of "branched evolution" stimulates fresh thought on the relevance of timing of exposures in relation to subsequent cancer risk. For example, given that certain "driver" mutations may only exert their carcinogenic effects in the context

of favorable selective conditions at the level of the micro-environment, one can postulate that past exposures may leave genetic or epigenetic alterations that are only expressed far later in time, contingent on subsequent exposures. The fact that adult diseases such as cardiovascular diseases or cancer were influenced by previous exposure including in utero, e.g. nutrient deficiency in later generations due to the Dutch famine during the World War II [15], suggests that the whole lifecourse has an impact on adult disease. This poses particular challenges to the identification of risk factors that may exert a type of "hit-and-run" effect.

In sum, the most recent understanding of cancer etiology presents us with a complex scenario where disease (here, cancer) is the result of a process in which factors in the micro- and in the macro-environment interact. Such interactions are consistently found in the associations identified by studies in molecular epidemiology. The challenge for molecular epidemiology is therefore to explain how biological mechanisms across the micro- and macro-environment contribute to causal reasoning.

A philosophical understanding of cancer etiology

Biomarkers: the link between the macro- and the micro-environment

In order to causally link the micro- and macro-environments, omic technologies provide a key set of instruments in cancer research: these allow us to connect exposure and disease by finding the "right" biomarkers. Biomarkers are key in causal analysis in cancer research and play a major role in our conceptualization of cancer causation. This is well expressed in the diagram that connects exposure markers, early effect markers and susceptibility markers in the classical "molecular epidemiology" paradigm, as described in Schulte and Perera's [1] book and further elaborated recently [16].

In 1998, the National Institute of Health Biomarkers Definitions Working Group defined a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention." Biomarkers are largely *constructed* by cross-checking data that are generated by some machines (e.g. mass-spectrometry) and subsequently analyzed using other machines (computers and their algorithms). An important question therefore concerns the kind of *ontological status* that we should give to biomarkers. Strictly speaking, they don't seem to be just 'objects out there'. Schulte and Perera [1] describe biomarkers in terms of 'events' in the continuum from exposure to disease. But even within this continuum, such markers may represent a genuine event (e.g. direct exposure to a pollutant), may be correlated with such an event (the classical example of yellow fingers in heavy smokers), or even be a predictor of the event without being causally associated to it (like the association between two X chromosomes and the propensity to wear skirts). The fact that biomarkers are hardly corresponding to "causal" molecular entities does not imply that they cannot be measured. In fact, this is what molecular epidemiology routinely does. But, as Schulte noticed as early as 1993, there are multiple ways of defining and measuring biomarkers, which raises the question of their ontological status.

The issue gets even more complex because molecular epidemiology is not interested in finding biomarkers *per se*, but in understanding the *continuum* of disease development from early exposures, via finding biomarkers. Similarly, in other contributions, the technologies used to detect biomarkers (some of which are called omic technologies) are said to provide the 'missing link' between exposure and disease or, given the previous discussion, between the macro- and the micro-environment [17–19].

This conceptualization of biomarkers search—i.e. as the continuum linking exposure and disease—emphasizes *processes* rather than *things* or *objects*. This calls for two remarks. On the one hand, biomarkers are not entities, things to which we can attribute some causal power, in the same sense as HPV virus has the power to initiate the onset of cervical cancer. Instead, biomarkers are clues, indicators, *markers* to detect in order to reconstruct the missing link. On the other hand, and related to the previous point, we need to say in which sense, if any, these continuous links, or processes, between exposure and disease are *causal*. This is all the more important because we seek to link *heterogeneous* levels as the macro- and the micro-environment. In sum, our approach aims to address two main questions: first, how to understand causal *production* from the macro- to the micro-environment, and second, why it is important to have a coherent conceptualization of such causal links. We discuss these two issues in reverse order: spelling out the second question will provide further motivation for our approach.

Information transmission and the link between macro- and micro-environment

Finding a coherent conceptualization of the link between the macro- and the micro-environment is important for the following reason. The macro-environment consists of biological agents, pollutants and chemicals we are exposed to, but also of social interactions and "psychosocial factors". The micro-environment, instead, is made of biochemical and molecular processes measured at different "omic levels". How to make the causal link between the macro- and the micro-environment plausible, beyond a "coarse-grained" difference-making relation between the two?

By and large, traditional epidemiology has done this successfully for a long time: establishing robust associations between classes of exposures and classes of diseases. But with the advent of molecular epidemiology, these associations also relate factors at very different levels (the micro and macro environments). This rests on a *change of the scale of measurement*: environmental exposure has traditionally been assessed by measuring the *levels* of individual chemicals in, say, air or water. Thus newer finer-grained measurements initially try to restore some kind of "scale homogeneity": measure the level of a pollutant or of a chemical externally and then measure changes at genomic, transcriptomic, proteomic, or metabolomic levels internally. Although 'scale homogeneity' is restored through making all measurements chemico-biological measurements, the problem is not solved.

In fact, measurements now taking place at the same level allow the researcher merely to establish another association or series of associations (difference-making relations), albeit at a much lower level now. For instance, we might establish a robust correlation between the level of a certain chemical in the air and the biomarker of early clinical changes of a targeted disease (lung cancer). But this doesn't establish a *causal link* yet. It only estimates a more precise measure connecting levels of hazards and levels of omic changes. On the one hand, to establish a causal link we still need to find the right "intermediate" biomarkers, the ones that are linked to exposure and to disease. To be sure, this search (finding appropriate biomarkers) obviously relies upon studying associations, e.g. via omics analyses. On the other hand, we need to place this reconstructed link into a plausible network of relations (i.e. the mechanisms of carcinogenesis described in the first part of the paper), and this is precisely the kind of 'biological thinking' mentioned earlier. It is important to note that linking, here, cannot be seen by the naked eye, and not even using sophisticated experimental setups. Instead, the scientist reconstructs the linking by putting together the pieces of the *evidential puzzle*, just as a crossword puzzle [20]. Biological theory needs to be complemented with the results of omic analyses, which in turn need sophisticated and complex statistical analyses. It is in this sense that cancer etiology needs a *plurality of evidence* from which to make causal inferences. All this requires considerable empirical evidence and much *interpretation* of the evidence using the appropriate concepts. One such concept is *information transmission,* as we argue later.

A second, more important, reason why the problem is not solved is that although homogeneity in the scale of measurement is restored by using biological measurements, this makes the results harder to interpret, because the interpretation still has to identify causes at the macro level, i.e. the level of environmental exposure causing disease. We need this causal knowledge to design appropriate public health interventions. To sum up: we measure everything at the micro-level (level of pollutant, and level of metabolite) but ultimately what we want to know is how and to what extent environmental pollutants or psycho-social factors cause diseases. The problem molecular epidemiology faces is: how can we understand macro-factors causing micro-factors, or vice versa? What we have to establish is a continuous linking, not just (finer-grained) correlations at a different level of measurement. Continuous linking can be conceptualized as information transmission, as we explain next.

Productive causality as information transmission

We mentioned earlier that causal claims about exposure and cancer involve statements about risks, i.e. *difference-making*: whether certain exposures are good predictors of disease, at different stages of disease development, or at different stages of life, etc. Simultaneously, we also look for evidence about *how* exposure leads to developing disease. Typically, 'how' exposure leads to disease has been understood in terms of the mechanisms that produce disease, mainly with the study of biomarkers. Mechanisms provide us with information about how causes *produce* effects. This position is called, in philosophy, *evidential pluralism*, to emphasize the need for multifold (or multilayered) evidence in order to establish causal claims [3]. A prestigious example of evidential pluralism is the joint use of epidemiological evidence (difference-making) and mechanistic evidence (productive causality) in the Monographs of the International Agency for Research on Cancer [21].

The difference-making component of evidential pluralisms is, in a sense, less controversial than the productive component, as even theorizers of agnostic data-driven approaches will agree that the search for robust statistical associations lies at the very heart of data-intensive science. What remains controversial is what biomarkers are marks *of* within a mechanistic understanding of cancer etiology. This is problematic because, as discussed before, we want to establish links between macro- and micro-factors. On the one hand, causal relations are not reduced to bio-chemical relations and, on the other hand, they are not mere (finer-grained) statistical associations among macro-variables.

If the causal link connects factors at different scales and of different types, then the notion of productive causality (i.e. how causes and effects are linked) needs reconceptualization. But the type of linking sought may be different depending on the scientific context or the purpose of the causal question.

There are several candidates for characterizing links; we mention the two most prominent here. First: Wesley Salmon's "mark transmission theory" [22–25]. In Salmon's view, the central question is how to distinguish between *causal* processes and non-causal (or pseudo) processes. Simply put, causal process transmit marks, while pseudo-processes don't. Think about what happens when introducing a mark in a process: if the process is causal, the mark persists at a later stage. A stock example is denting a car, and observing that the dent is transmitted along with the movement of the car, while its *shadow* will not further transmit the mark. This shows that the moving car is a causal process, while a moving shadow is not. However, not every process can be marked, and Salmon formulated the approach in counterfactual terms: a casual process is one that *could* be marked and that *could* transmit the mark. Causal processes, in this approach, are those transmitting physics quantities, such as energy or momentum (think of billiard balls colliding). However, this approach is tailored to physics and does not provide the conceptual tools to understand the macro–micro linking mentioned above. Second: the 'complex-systems' approach [26]. According to this approach, to establish causal relations one needs to identify mechanisms, in the sense of complex systems that link causes and effects. Such approach, however, emphasizes the *organization* of different components of a mechanism, rather than the *continuum* linking exposure to disease. For instance, a mechanistic explanation sheds light on the way a gene normally is methylated, and how it is hypomethylated when exposed to tobacco smoking. We can shed light on these mechanistic aspects by identifying the relevant molecular entities and activities involved, and their *organization*. But this is not very illuminating about the continuous link between exposure and disease, that is the *process* initiated with exposure and that eventually leads to disease development, via several intermediate stages.

The link is instead better conceptualized using the notion of "information transmission". Note that information transmission does not coincide with transfer of biological information between macro- and micro-factors. Instead, information transmission refers to how the scientist reconstructs the linking between macro- and micro-factors, putting together all the available pieces of the evidential puzzle. In other words, information transmission is at the level of epistemology, not of ontology.

In a previous article [27] we suggest that we need to explore the prospects of the notion of information that comes from the way scientists themselves explain the role of biomarkers; in this context, the idea of 'picking up signals' recurs, for instance:

> *From these two parallel analyses [statistical analyses], we obtained lists of putative markers of (i) the disease outcome, and (ii) exposure. These were compared in a second step in order to identify possible intersecting signals, therefore defining potential intermediate biomarkers [28].*

What is the *signal* that we have to pick up? In what sense will this give us the sought production-relation between exposure and disease? Our suggestion is to conceptualize the detection and tracing of signals in terms of *information transmission*, as sketched above. This, we submit, is a generalization of Salmon's mark transmission theory [27].

The key difference with Salmon processes consists in the marking aspect. Salmon's approach rests on the *introduction* of the mark. However, in most cancer research we look for *existing* marks from exposure to disease that transmit along the process, without introducing them ourselves. Cancer research is largely an observational rather than an experimental science.

This understanding of causal production as information transmission takes full advantage of a conceptualization in terms of mark transmission in processes, without being tied to the quantities of physics, say energy or momentum, being transmitted. It also takes full advantage of a conceptualization in terms of mechanisms, because knowledge of relevant molecular or biochemical mechanisms will indicate where to look for signals, for instance choosing appropriate omics levels for the analyses of biological specimens. In this sense we say that mechanisms are *information channels:* "biochemical or molecular spaces" where we look for the flow of information that we try to intercept using biomarkers [27].

Ultimately, we want to understand the whole phenomenon of carcinogenesis: all the relevant omics levels involved, how they interact, and build reliable models of the dynamic evolution of whole systems under many different exposure conditions. The concept giving the dynamic evolution is *information transmission*. The flow is in the link, and the link, as suggested, is best thought of as informational. More precisely, it is given by the *scientists' reconstruction* of the information transmission through the different types of analyses, i.e. by putting together all the pieces of the "evidential puzzle".

The question remains: what exactly does information mean? In Genome Wide Association Studies (GWAS), there is at least some possibility of a clear (univocal) definition of information, as genes are more clearly defined than in most omic measurements, and substantive informational concepts make sense when applied to genes. Instead, in Exposome Wide Association Studies (EWAS) information is still not well-defined [27].

(Often omic "signals" are only "features", i.e. they need to be decoded after discovery). However, the diversity and richness of informational concepts (many of which currently being developed and discussed), is not a weakness of an informational approach, but a virtue. This is captured, for instance, by philosophical accounts, especially those developing *qualitative* notions of information. One such account is *semantic* information, namely what the observer (here, the scientist) can process, looking at the data, omic analysis, biological theory, etc. It is in this sense that information transmission cannot be reduced to biological information, but it is certainly part of it.

One advantage of information transmission is that it is capable of offering a structure for thinking about how heterogeneous factors such as micro and macro-biological and social—are linked; this is a pressing issue in the light of results of omic studies and also for the design of public health policies.

Conclusions

Systems biology is driven by technology (the development of omics) and by statistical modelling and bioinformatics. It is high time to bring biological thinking back. To address the new challenges of epidemiology, the concept of the "exposome" has been proposed, initially by Wild et al. [14], and then expanded by others, particularly Rappaport and Smith [29] who functionalized the exposome in terms of chemical signals detectable in biospecimens. This is consistent (and in fact is an extension) of previous work on molecular epidemiology by e.g. Schulte and Perera [1]. The canonical exposome concept refers to the totality of exposures from a variety of sources including chemical agents, biological agents, radiation, and psychosocial components from conception onward, over a complete lifetime [24]. We offered a unifying framework to incorporate omic data into causal models, using the position called "evidential pluralism": causal reasoning is based on both "difference-making" and the underlying biological mechanisms. In particular, we conceptualize the way scientists detect and trace signals in terms of *information transmission*, which is a generalization of Salmon's mark transmission theory. One advantage of information transmission is that it is capable of helping us conceptualize how heterogeneous factors such as micro and macro-biological and psycho-social—are causally linked. What we want to make clear is that—though it is often thought that going down the molecular level means to add details to a macro-level causal relations—this is in fact not the case. A good example in this respect is epigenetics, which shows that the way in which the macro is causally linked to the micro is not simply a matter of adding details to the same mechanism, but a matter of transmission of information from outside the body downstream to DNA and then the informational chain in the cell. This is important not only to understand cancer etiology, but also for the design of public health policies. In fact, public health interventions cannot target biomarkers, but the right causal factors at the macro-level, such as environmental hazards and socio- economic and psychological factors.

Additional files

Additional file 1: Figure S1. Branched evolution (3).
Additional file 2: Figure S2. The macro-environment: ecology of cancer in a historical perspective. Examples are purely illustrative.

Authors' contributions

All authors equally contributed to the work. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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Exhibit 123

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Evaluating intrinsic and non-intrinsic cancer risk factors

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Discriminating the contribution of unmodifiable random intrinsic DNA replication errors ('bad luck') to cancer development from those of other factors is critical for understanding cancer in humans and for directing public resources aimed at reducing the burden of cancer. Here, we review and highlight the evidence that demonstrates cancer causation is multi-factorial, and provide several important examples where modification of risk factors has achieved cancer prevention. Furthermore, we stress the need and opportunities to advance understanding of cancer aetiology through integration of interaction effects between risk factors when estimating the contribution of individual and joint factors to cancer burden in a population. We posit that non-intrinsic factors drive most cancer risk, and stress the need for cancer prevention.

The past few decades have seen significant progress in our understanding of cancer aetiology as well as advances in early detection, treatment, and prevention[1–3], which have led to declining cancer mortality in the industrialized world. Despite this progress, certain cancers continue to increase in different parts of the world due, in part, to longer lifespans and changing patterns of cancer risk factors[4]. This includes the first evidence of impacts of the obesity epidemic on cancers[5]. Furthermore, significant gaps in age-adjusted cancer incidence rates for nearly all cancers across different regions of the world suggest that much of cancer risk is due to causes other than unmodifiable intrinsic DNA replication errors common to all humans which we define as the 'intrinsic risk'[6].

Extensive efforts over several decades have been directed at and continue to be expended on identifying risk factors for cancer. For several cancers, aetiology has been convincingly linked to specific environmental factors resulting in effective cancer prevention (https://www.cancer.gov/about-cancer/causes-prevention/risk), e.g., smoking and lung cancer, sun exposure and skin cancer, human papillomavirus (HPV) and cervical cancer, *Helicobacter pylori (H. pylori)* and gastric cancer, and viral hepatitis and hepatocellular cancer (HCC).

While certain external exposures have been established in cancer causation, the contribution of random errors in DNA replication has been more difficult to estimate. Two recent modelling studies suggested that over 60% of tissue cancer burden may be due to factors that are intrinsic to human cell biology and thus, not modifiable[7,8]. This conclusion has been highly contested[9–15]. Nevertheless, these provocative findings gained media attention as evidence dampening healthy behaviours for cancer risk reduction and renewed old debates on the role of modifiable factors in cancer causation among scientists. They also raised questions about the evidence that scientists

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use and assumptions that they make to mathematically estimate the contribution of different factors to the burden of cancer in the population setting.

Here, we briefly introduce and refine the definitions of intrinsic and non-intrinsic risk factors that have been employed in these recent works and how evidence for their effects on cancer burden in human has been obtained considering the type of study (observational or experimental). This includes a discussion of the assumptions about cancer aetiology that have been used to estimate the contribution of various factors to the burden of cancer in the human population. Through clarifying the definitions, and analyzing the cumulated models, data, and findings from historical and modern literature, we develop our position that non-intrinsic factors are the major contributors to cancer risk and thus open the door for significant prevention.

Cancer risk factors and cancer risks

The pursuit of cancer risk factors has been instrumental in the development of both data-driven analytical approaches and theory-driven models for carcinogenesis. The former was initiated by landmark epidemiological studies of lung cancer and tobacco smoking in the 1950's. The latter began with the modelling of carcinogenicity in animals early in the 20th century[16–18] and subsequently in humans[19–26], culminating in two recent contrasting models that we highlight below[8,15].

To facilitate the discussion and relate to recent published model-based estimates, separate categories for cancer risk factors are defined below based on their biologic nature, modifiability and use in the literature (Fig. 1):

(1) Unmodifiable intrinsic risk refers to unavoidable spontaneous mutations that arise as a result of random errors in DNA replication related as a characteristic of being human. These unavoidable DNA replication processing errors occur in different organisms at different rates as a species specific, random replication error rate.

(2) Non-intrinsic risk refers to factors that include: (2a) Modifiable exogenous/external factors (e.g., carcinogens, viruses, xenobiotic) and lifestyle factors (e.g., smoking, hormone therapy, nutrient intake, physical activity) that are exogenous to the host; and (2b) Endogenous factors that are partially modifiable and related to the characteristics of an individual (e.g., immune, metabolism, DNA damage response, hormone levels) and influence key aspects of cell growth control and genome integrity.

Intrinsic risk factors	Non-intrinsic risk factors	
	Endogenous risk factors	Exogenous risk factors
❖ Random errors in DNA replication	❖ Biologic aging ❖ Genetic susceptibility ❖ DNA repair machinery ❖ Hormones ❖ Growth factors ❖ Inflammation ❖ etc.	❖ Radiation ❖ Chemical carcinogens ❖ Tumour causing viruses ❖ Bad lifestyles such as smoking, lack of exercise, nutrient imbalance ❖ etc.
[Unmodifiable]	[Partially modifiable]	[Modifiable]

Fig. 1 Three types of cancer risk factors. The overall cancer risk factors are divided into two mutually exclusive components: the unmodifiable intrinsic and the modifiable, at least partially, non-intrinsic risk factors. The intrinsic risk factors refer to random errors resulting from DNA replication. The non-intrinsic risk factors further consist of endogenous and exogenous risk factors depending on whether such factors are more internal or external to an individual

We have selected these definitions to assure better dissection of the contribution of 'intrinsic errors' as an unmodifiable risk factor for cancer modelled in recent studies[27,28]. Particularly, this definition of intrinsic risk implies three corollaries of high relevance to additional analyses: (1) The contribution of this unmodifiable risk to cancer incidence should be constant across populations since all humans have the same intrinsic mutation rates; (2) This contribution should also be consistent over time since the underlying mechanism is a property of the human species; and (3) the contribution of intrinsic DNA replication errors to mutational signatures should be constant across tissues and organs.

In addition, it should be noted that cancer displays a complex etiopathogenesis and that these various factors interact in tumour evolution (e.g., gene–gene or gene–environment interactions). For modelling and discussion purposes, cancer risk types have been discretized as the intrinsic risk and the non-intrinsic risk, which refers to all risk minus the intrinsic risk, or likewise, the sum of risks due to non-intrinsic factors, plus their interactions, plus the interactions between intrinsic and non-intrinsic factors. Accordingly, this definition of intrinsic risk accounts for those cancers where intrinsic error is sufficient for tumorigenesis. Thus, in deriving the intrinsic risk (so-called 'bad luck'), one must subtract risk not only due to individual non-intrinsic factors, but also to their interactions with intrinsic factors. This group would include cases where the intrinsic factor (i.e., basal mutation rate) contributes and may be necessary but not sufficient. As an example, a specific lung cancer may arise from three driver mutations, one of which arises from an intrinsic error and two from mutagens in tobacco smoke. In this case, the intrinsic error is necessary but not sufficient for detectable invasive carcinoma to develop. From an intervention point of view, this is critical as preventing the modifiable component (i.e., smoking exposure) would still be effective in preventing cancer in these settings.

Intrinsic risk factors

As defined above, intrinsic risk arises from the basal mutation rate operating in all dividing cells, in the absence of any non-intrinsic factors.

We have chosen to define unmodifiable intrinsic risk in this narrow way as it corresponds to a biologically intrinsic factor that causes DNA mutations in humans that is not modifiable. Thus, all humans are 'stuck' with this risk, unlike other sources of non-intrinsic factors that may vary between individuals.

Passage or fixation of randomly acquired mutations (e.g., single nucleotide errors, deletions and insertions) in a tissue is dependent on the survival and division of the mutated cell and its progeny. These mutations may yield "driver mutations" required for cancer development, in distinction from "passenger mutations" that do not impact cancer formation but are found commonly in cancers. A requirement for more than one driver mutation to initiate cancer increases the barrier to develop cancer with intrinsic mechanisms alone.

In 2015, Tomasetti and Vogelstein asked why different tissues exhibit dramatically disparate cancer rates. Using estimates of the number and dynamics of tissue-specific stem cells for 31 tissue types, they observed a strong correlation between estimated stem cell divisions and lifetime cancer risk at log10 scale. From their modelling work, they suggested that a significant and underappreciated component of cancer risk, as much as 64%, may be due to unmodifiable random errors in DNA synthesis or bad luck[7]. This hypothesis sparked debates[9,13] on the nature of this correlation and its implications for causality of stem cells in cancer pathogenesis. In our work, we found that the correlation between stem cells and cancer risk does not distinguish the

operation of intrinsic from non-intrinsic factors and vice versa, since many non-intrinsic factors (e.g., smoking) induce their own mutations, and the likelihood of induction and propagation of these mutations also correlates with tissue cell divisions[15]. Thus, tissues with much larger cell divisions are susceptible to higher intrinsic mutations as well as to higher mutations induced by external factors. This conclusion was supported in recent analysis by Nowak et al.[29]. Furthering the complexity of cancer risk factors, in one study, Klutstein et al.[30] found a stronger correlation between tissue levels of DNA methylation and cancer burden. This correlation persisted even after correcting for the contribution of stem cells whereas the reverse did not hold. These authors concluded epigenetic changes, which can be influenced by exogenous and endogenous factors, and not only mutations contribute to cancer risk with a similar dependence on the number of cell divisions in a tissue. Thus, while these *correlative* studies support total tissue cell division in the observed variation between tissue-specific cancer risks, this association is correlative and only explains a part of that risk.

Mutational signatures in human cancer reveal past events. The direct estimation of intrinsic error to cancer risk is challenged by the technical inability to truly separate intrinsic errors from the effects of non-intrinsic factors in humans. Evidence for intrinsic risk in cancer has historically relied on modelling studies of cancer development based on experimental/clinical data. The recent advent and rapid development of next-generation DNA sequencing technology has revolutionized the ability to survey genome-wide somatic mutations in cancer. Analyses of these data are providing new insight into the role of intrinsic versus non-intrinsic cancer risk factors, and in some cases, linking specific signatures to specific risk factors. Here we discuss recent work from large-scale tumour sequencing studies applied to estimating the magnitude of intrinsic risk and its contribution to human cancer.

Using genome sequence data, more than 30 distinct mutational signatures were recently uncovered in different cancers[31]. Of these, 10 can be associated, at least partially, to known mutagens. Interestingly, two signature mutations demonstrated strong positive correlations with age in most cancer types, indicating that they are acquired at a relative constant rate over the lifetime of cancer patients, regardless of tissue of origin. This pattern is most consistent with the action of an intrinsic error process, since errors arising with DNA replication during cell division would accumulate in a monotonic fashion over time. In contrast, the other signature mutations lack a consistent correlation with age, suggesting they may be acquired at different rates in life due to different influences[31]. Since all known carcinogen-specific signatures demonstrate an age-uncorrelated and tumour-specific pattern, it is reasonable to assume those with unknown causes are also a consequence of external exposures to DNA damaging agents.

Based on this segregation of signatures, the proportion of cancers driven by intrinsic risk can be calculated, as shown in Box 1, to account for no more than 10–30% of all cancer incidence[15]. Notably, a number of cancers, such as lung and skin cancer, with substantial environmental risk as determined from epidemiologic studies, also contain large percentages of non-intrinsic risk estimated from the mutational signature data (Extended Data Table 3 in ref. [15]), supporting the validity of this approach.

Modelling of contribution of intrinsic mutations. Several studies have attempted to estimate the number of driver mutations required for the development of an invasive carcinoma. The emerging consensus is that at least three hits are necessary for solid tumours and fewer for haematologic malignancies. The historical development of this work is shown in Box 2.

Replication error rate is a critical parameter in modelling intrinsic cancer risk in human cells, and the unrepaired error rate has been estimated at $\sim 5 \times 10^{-10}$ per nucleotide site per cell division[32]. This corresponds approximately to three new mutations per genome per cell division. Replication error rates between different cell types in an organism are roughly constant given the fundamental nature of the replication process. For proto-oncogenes, gain-of-function mutations typically occur at specific sites that increase action of the target protein (e.g., $JAK2^{V617F}$ or $KRAS^{G12V}$). In contrast, loss-of-function mutations can occur at multiple sites whereby numerous mutational events

Box 1 | Mutational signatures and cancer risks

Sequence analyses of large cancer genomic data suggests that for some cancers, mutations are not random and dependent on the nucleotide context around mutation sites. Such mutational signatures are sequence patterns preferably associated with specific mutagens and are regarded as 'fingerprints' left on cancer genomes by different mutagenic processes. For example, because UV radiation usually induces formation of covalent links between two adjacent pyrimidines, C>T mutations due to UV occur mainly at dipyrimidine sequences[81]. More than 30 distinct signatures have been identified so far, and several of them have been mechanistically associated with known risk factors such as UV radiation and smoking. A few signatures demonstrate strong positive correlations with age in the majority of cancers, suggesting they likely arise from some fundamental tissue-independent and constant intrinsic biological processes, such as replicative errors in cell divisions.

These data can be used to estimate (1) the percentage of mutations due to intrinsic factors, and (2) the intrinsic risk. Suppose the percentage of intrinsic mutations in a specific cancer is p, and n driver mutations are needed for cancer onset. Intrinsic risk is then defined as the probability of incurring the n driver mutations with intrinsic mechanism only and can be calculated as

$$Intrinsic\ risk = (cancer\ incidence) * p^n.$$

For example, when $p = 0.5$, n=3, and cancer incidence = 1%, the intrinsic risk is then 1% * 0.125 = 0.00125. Similarly, using the binomial distribution, one can compute risk due to extrinsic factors alone, and risk due to the interactions between intrinsic and extrinsic factors. It should be noted that not all carcinogens are mutagens, and therefore would not leave signatures on genomes. However, it has been observed that many cancers known to have substantial environmental risk proportions, such as breast cancer, colorectal cancer and melanoma, all harbour large percentages of total extrinsic mutational signatures. More interestingly, for cancers such as acute myeloid leukemia (AML) and acute lymphocytic leukemia (ALL), that do not have strong epidemiology support for their environmental causes, their intrinsic risks calculated from mutational signatures are relatively high.

The current non-intrinsic cancer risk estimates from the mutational signature data assumes that the intrinsic and extrinsic mutagenic mechanisms have the same probability of inducing mutations in cancer driver genes. Biased estimations may arise if such an assumption is unattainable. In addition, more than 900 chemical agents have been evaluated by the International Agency for Research on Cancer (IARC), of which more than 400 have been identified as carcinogenic, probably carcinogenic, or possibly carcinogenic to humans[124]; however, mutational signatures for these mutagens remain largely unidentified. Uncovering these would further improve the accuracy of the estimated cancer risk distributions.

Box 2 | Number of driver mutations required for cancer pathogenesis

A stochastic multistage model of carcinogenesis has served as the primary biological theory of cancer for a century. This theory evolved from the early studies of carcinogenicity in animal models and incorporated analysis of cancer incidence in human populations[20,125]. Early work by Yamagiwa and Ichikawa[18] showed that malignant tumours develop through multiple steps for which, carcinoma development and metastasis were late events dependent on chronic irritation. It was subsequently demonstrated by several groups that tumorigenesis required both exposure to an initiating carcinogen and the presence of tumour promoting factors[16,17]. This initiator/promoter model of tumorigenesis motivated Charles and Luce-Clausen[125] to posit that the transition from normal cell to early tumorigenesis (papilloma) involved two mutations in a single gene and that carcinogens acted to accelerate the mutation process that would otherwise be rare, i.e., the gene mutation theory. Muller subsequently provided the evidence for the gene mutation theory demonstrating that ionizing radiation, known to be carcinogenic, was also mutagenic. Importantly, the observed latency between radiation exposure and cancer development supported the prevalent hypothesis that more than one mutation per cell was necessary for cancer development[20,21]. Observing an increase in cancer by the sixth power of age, Nordling proposed that cancer may require as many as six consecutive mutations[19]. Building on these works, Armitage and Doll[20] represented these concepts mathematically as a stochastic multistage carcinogenesis model using a pure birth process finding that the model fit best with six stages analysing the age-specific cancer incidence for several cancers. Subsequently, Knudson[22] published his two-hit model for retinoblastoma with his theory proven true with the discovery of the retinoblastoma tumour suppressor gene (Rb) in patients with retinoblastoma[23].

Moolgavkar-Venzon-Knudson (MVK) developed a much used clonal expansion model based on the two successive mutation hypothesis (initiator and promoter) in which they allowed for the possibility that only some cells survive after the first mutation and that cells grow at different rates (semi-stochastic model)[126]. This two-stage model was extended to multiple stages in 1995[24] in a Frequentist maximum likelihood estimation framework, and more recently to a Bayesian framework[25].

The earliest effort to estimate the contributions of initiators and promoters on carcinogenesis is attributed to Moolgavkar[127]. In his work, initiator was 'any' factor that increased the probability that a normal stem cell would transition to a cell with one hit. A promoter was defined as an agent that promoted the expansion of the 'intermediate' cells. Considering age incidence curves, he demonstrated that two cancer risk factors (smoking for lung and oestrogen for breast cancer) modulate tumorigenesis by increasing the transition rate for the promoter rather than the initiator. Analysing the Japanese atomic bomb survivors, Heidenreich and colleagues[26] extended the multistage model to account for an acute exposure to a mutagen using an age-dependent hazard rate. Indeed, multistage models can be readily extended using discrete or continuous stochastic processes, analytical or numerical methods, to accommodate modern cancer theories.

More recent studies from large-scale sequencing data on cancer genomes suggest that three driver mutations may be sufficient for cancer development for some/most solid tumours[128]. Fewer hits may be required for haematologic malignancies (i.e., cancers of the blood, mostly leukaemias) as bone marrow and blood derived cells need fewer steps to become cancerous, e.g., no requirements for invasiveness and metastatic potential. For example, chronic myelogenous leukaemia (CML) originates with only one mutation[129], although at this stage CML is a more 'benign' cancer, and other mutations are required as CML transitions to a more malignant/lethal phenotype[130].

promote gene loss or dysfunction (e.g., P53 mutations). Thus, the probability of mutating at least one cancer relevant gene is larger than the somatic mutation rate of one nucleotide. For example, if 20 mutable sites correspond to one cancer relevant hit, the probability of that hit would be 1×10^{-8} per cell division.

Based on these and related data, we developed a discrete stochastic multistage cancer stem cell model, with the model parameters (number of stem cells, intrinsic mutation rate, and the generations of symmetric versus asymmetric divisions) estimated from the most recent literature[15]. Once the intrinsic risk due to replication errors was computed, the difference between the model estimation and the observed epidemiological cancer incidence provided an estimate of the non-intrinsic risk (residual risk). These results suggested that cancer risk due to intrinsic factors alone is very low for cancers requiring more than two hits, consistent with other independent analyses including observational studies and a mutational signature study. Based on these data, we concluded that intrinsic risk explains at most 10–30% of all cancers[15].

More recently, Tomasetti et al.[8] published a new estimate of the proportion of cancer driver gene mutations due to intrinsic factors. For 32 cancers examined, they concluded that 66% of mutations were attributable to intrinsic causes. A major cornerstone of this recent work was the calculation of the intrinsic risk as the amount of risk that remains after subtracting effects of known environmental and hereditary factors. That is, the percentage of mutations due to intrinsic factors was computed as:

$$(\text{Percent due to})\ \text{Intrinsic} = 1 - \text{known environmental} - \text{known hereditary}$$

However, this approach inflates the effect of intrinsic factors by assuming there are no other non-intrinsic cancer-causing factors

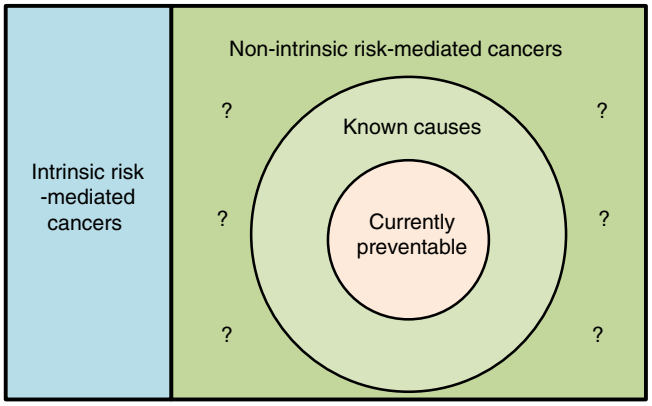

Fig. 2 This diagram illustrates the relationship between intrinsic and non-intrinsic risks, as well as preventable cancer and overall cancer burden. One can see that by ignoring the unknown non-intrinsic risk (area marked with?), the estimated intrinsic risk in ref. [8] is inflated as the true intrinsic risk (blue region) plus the unknown non-intrinsic risk. Preventable cancer is a subset of cancers with known non-intrinsic causes since to be preventable, a cancer has to have a known and modifiable factor (e.g., Radon is a known factor for lung cancer but not much modifiable.) By the same rationale, preventable cancer is often under-estimated due to the unknown non-intrinsic risk factors

to be identified. Inclusion of a yet to be identified non-intrinsic factor can significantly drive down the contribution of the intrinsic factors as illustrated in Fig. 2. For lung cancer, while Tomasetti et al. estimated the mutation fraction due to intrinsic factors at 33.4%; based on our mutational signature analysis, we identified a much smaller estimate (3.6%) of the intrinsic mutation fraction or a 9-fold difference[15]. This discrepancy could be due to the exclusion by Tomasetti et al. of known exogenous

risk factors for lung cancer including radon, a risk prevalent to the entire population and second only to cigarette smoking[33], as well as second hand smoking and air pollution[34,35] and yet to be determined environmental and hereditary factors.

Non-intrinsic risk factors

Mechanisms of non-intrinsic risk factors thought to drive cancers are multifaceted. Some belong to the family of chemicals that induce new mutations (mutagens) while others, such as viruses, induce cancers through activating or repressing key cancer modulating genes (activating oncogenes or inhibiting tumour suppressor genes) in addition to inducing mutations. At least in the case of mutagens, these operate on cells that can divide and persist so as to facilitate tumour development. In defining such 'at risk' cell populations, biologic studies have focused on stem cells, progenitor cells, and other dividing cells[36]. In the definition proposed here 'non-intrinsic factors' refer to risk factors other than intrinsic replication error, and includes not only exogenous factors (e.g., tobacco, HPV, ultraviolet (UV) radiation, and drugs) but also endogenous factors, such as inflammation, hormones and growth factors, metabolic effects, reactive oxygen species, immune responses, etc. The evidence for non-intrinsic risk factors is mainly derived from studies in cancer epidemiology and cancer biology.

Exogenous risk factors

Several landmark epidemiological and biological studies have identified exogeneous cancer risk factors such as tobacco smoke for lung cancer, UV radiation for skin cancer, and viruses for cervical and liver cancer. More recently, several groups have reported rising colorectal cancer incidence and mortality rates in Asia approaching those in western countries. Affluent Eastern Asian countries such as South Korea, Singapore, and Japan have experienced a two-fold to four-fold increase in incidence in recent decades[37]. In the USA, a recent study confirmed prior estimates that adults born in 1990 could experience twice the risk of colon cancer and four times the risk of rectal cancer at the same age had they been born in 1950. The reasons for the rise in incidence and death rates remain unclear[38] but cannot be attributed to change in factors intrinsic to DNA replication machinery in humans and thus, strongly indicate a role for non-intrinsic factors.

Geographic variation and immigrant studies. Evidence for causes of cancer in human populations has historically been guided by information on cancer incidence and prevalence rates in different populations. According to GLOBOCAN[39], incidence rates of different cancers show distinct geographic patterns where estimates in high-incidence regions can be as much as one or two orders of magnitude higher than low-incidence areas. Consistent with this pattern, we recently analysed the World Cancer Registry data[6] and found that the age-adjusted incidence rates of most cancers show distinct geographic patterns where estimates in high-incidence regions can be as much as ten folds or more than low-incidence areas[6]. Some examples, obtained by taking the ratio of the incidence rates at the 90th percentile and the 10th percentile, include: melanoma (40 fold), colorectal cancer (three fold), lung adenoma (seven fold), breast cancer (three fold), and prostate cancer (nine fold). The difference in world cancer incidence rates and wide disparity are shown in Fig. 3 (originally published in ref.[6]). As shown in this figure, the fold changes will be more dramatic if the ratio is between the regional maximum and minimum.

Favouring environmental risks, seminal work demonstrated that the offspring of immigrants to high incidence regions acquire the incidence patterns of the host country in one or two generations[40]. This adoption of the host country incidence pattern is consistent with changes in factors present in each geographic region. Indeed, higher incidences of lifestyle-related cancers (e.g., breast, prostate, colorectal and lung cancers) have been observed in the early industrialized countries. In contrast, higher incidences of infection-related cancers (e.g., cervical, stomach and liver cancers) have been observed in less developed regions and in areas with endemic infectious agents.

Retrospective case-control studies. Numerous hypotheses about the role of environmental exposures and cancer have been generated using retrospective case-control studies, in which the association of exposures (e.g., smoking) with cancer can be

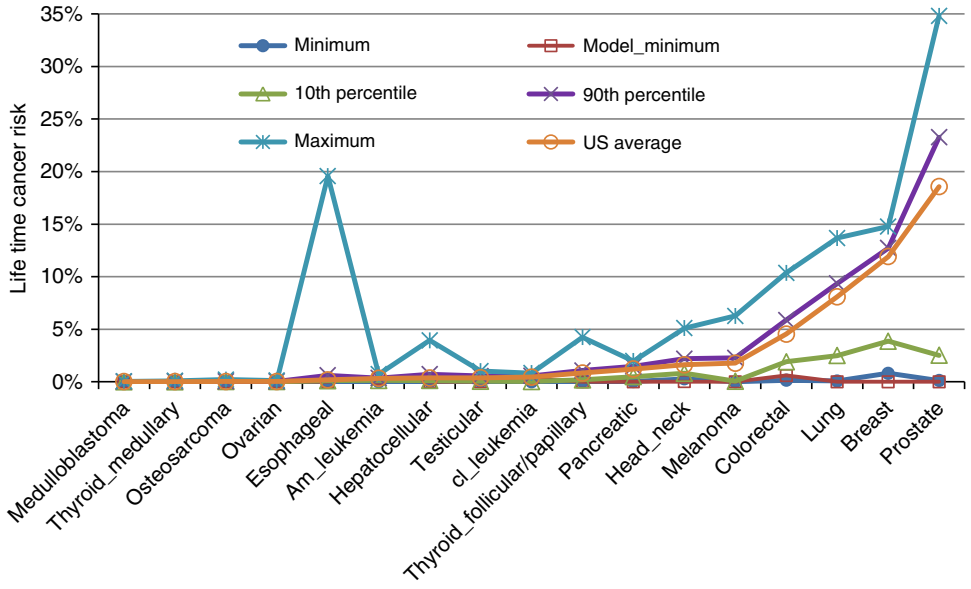

Fig. 3 Shown are the (conservative non-zero) minimum, the 10th and 90th percentiles, the US average, and the maximum of the lifetime cancer risk based on World cancer registry, and the stem-cell-model based minimum[6]. The huge disparity between the US average and world minimum indicates that cancer is unlikely the end result of a universal endogenous carcinogenesis mechanism unaffected by exogenous factors (published with permission[6])

quantified. Suspecting tarmac or motor car fumes as the major causes for the increased incidence in lung cancer, Doll and Hill[41] undertook a historical case-control study in 1950. Comparing lung cancer patients with matched controls, they discovered tobacco smoking was strongly overrepresented in the cases. Their findings were subsequently confirmed in a prospective cohort of more than 30,000 British physicians[42]. Over the past several decades, numerous groups have employed the case-control design and odds ratio (OR), under certain assumptions, to estimate the preventable proportion of cancer risk that is attributable to a given exposure: For melanoma, risk ascribed to sun exposure is estimated at 65–86%, and for non-melanoma basal and squamous skin cancers, ~90% is attributable to UV[43]. Here, the attributable risk refers to cancer risk that is theoretically preventable. Additionally, >75% of oesophageal cancer, and >75% of head and neck cancer are attributable to tobacco and alcohol[44,45] and for the latter, a large fraction of residual risk now suspected to be attributable to HPV[46]. Using this approach, several pathogens (HPV, hepatitis B virus (HBV), hepatitis C virus (HCV) and *H. pylori*) have been identified as cancer causing explaining a majority of cancer of the cervix, liver, stomach and others[47–50].

Prospective studies. Supporting links between risk factors and cancer identified in case-control studies, numerous prospective studies have been conducted and proven highly informative. For example, prospective studies on lung[42], oesophagus and gastric[51], bladder[52] and other cancers[53,54], have confirmed the association of smoking in human carcinogenesis, particularly in the aero-digestive tract. The robustness of the associations has yielded reliable estimates of cancer risk among smokers. Using these estimates and knowledge of smoking rates, the prevalence of smoking-associated cancers has been approximated to be as much as 25–30% of all human cancers[55].

In the case of cancers associated with infectious agents[56], prospective studies of *H. pylori* and gastric cancer[57], HPV and cervical cancer[58] and recently head and neck cancer[59], as well as study of HBV and HCV in HCC[60,61] have yielded evidence linking these agents to tissue-specific cancers. It is currently estimated that infectious agents contribute upwards of 15–20% of all human cancers[56].

Other physical factors such as ionizing[62] or UV radiation[63] contribute causally to cancer incidence, and their linkage to cancer has led to effective preventive measures. High-dose mantle field radiation for the treatment of Hodgkin's lymphoma was demonstrated unequivocally through prospective studies to increase breast cancer especially those exposed at younger ages[64]. Other sources of ionizing (e.g., environmental radon) and non-ionizing (e.g., UV) radiations have also been linked to lung cancer[65], leukaemias and lymphomas[66], melanoma and other skin cancers[63]. These preventable exposures have been estimated to contribute to ~20% of cancers[67].

In addition to these defined exposures, more complex lifestyle and behaviour factors such as diet, physical activity, alcohol consumption and reproductive patterns have also been intensively studied in cancer risk using the prospective design. For example, physical activity and dietary patterns, particularly nutrient deficient and calorie-dense diets (i.e., high dietary fat, refined sugar, red and processed meats), have been positively associated with high-incidence cancers of modern society including colorectal[68], breast[69], prostate[70] and lung cancer among non-smokers[71]. However, data from prospective studies on specific essential nutrients (i.e., folate, calcium, vitamin D, and others) on cancer risk have been equivocal. The European Prospective Investigation into Cancer and Nutrition (EPIC) study[72] supports diet as an important or moderately important factor in risk of colorectal and breast but not prostate cancer.

In efforts to increase the sensitivity and reliability between individual dietary factors and cancer, epidemiologists have developed modern analytical methods[73,74]. Employing a meta-analysis of 53 retrospective epidemiologic studies comprising of 58,000 women, women who drank >45 g of alcohol per day were found to have a 1.5-fold higher risk of breast cancer than non-drinkers[75]. This finding was replicated in the Million Women Study in the UK[76]. Using such tools and data, diet has been estimated to contribute to 20–40% of all cancers[77,78].

While epidemiological studies have a number of strengths, certain inherent weakness limit the reliability of findings when present in only one or a few studies. For geographic comparisons of cancer risks, information on routine medical records and death registries tend to be less accurate or complete in less developed countries and less impacted by asymptomatic, screen detected cancers. This impacts the accuracy and interpretability of the rates. These factors may inflate findings of difference between countries. On the other hand, other considerations may obscure effects of environmental factors. For example, if common exposures exist globally, which may happen increasingly with globalization, it will be harder to recognize their contribution to cancer risk. For retrospective (especially) and prospective study design, confounding effects and selection biases affect the accuracy of the risk and the estimation of the effect size. As such, while replication of findings across studies is among the more powerful criteria for establishing an association, gaining knowledge of the biological mechanisms linking an exposure to disease is a necessary component of the evidentiary process in establishing direct causal relationships.

Despite these inherent limitations, population studies have provided convincing evidence for a major contribution of exogenous factors in cancer risk.

Mutagens and mutational signatures. Exogenous mutagens, such as UV irradiation, have long been recognized to induce specific mutation patterns in genomes[79]. However, it was not until recently that strong signatures were identified for tobacco[80] and UV light[81] in lung cancer and melanoma genomes, respectively. These also provided the proof of principle in discovering the effect of mutagens without knowing their origins. Particularly, capitalizing on many large consortia studies targeting sequencing of large numbers of genomes, such as The Cancer Genome Atlas (TCGA), several mutational signatures have now been identified and characterized with respect to a wide range of cancer types[31,82]. As discussed above (Box 1), this analysis suggests that non-intrinsic factors are dominant in imparting cancer risk. More importantly, given the rapid progress of sequencing technologies, new specific signatures are coming into light with new research that is assigning them to specific exposures. For example, aristolochic acid, common in east Asia and parts of Europe, has been shown to predispose to cancers of the renal pelvis, and is associated with a highly specific signature[83].

Endogenous risk factors

Certain cancer risk factors are endogenous to the individual and many have some genetic component. Individual levels of the sex steroid hormones and their role in breast cancer risk are among the best studied examples of an endogenous cancer risk factors[84]. As endogenous determinants of cancer risk, the steroid sex hormones vary over the life course and between individuals and are influenced by other exogenous factors (e.g., diet, therapeutic hormones, other drugs, physical activity levels) as well as other endogenous determinants such as genetic background. Importantly, endogenous sex steroid hormones and cell responses to

hormones are proven targets for cancer prevention supporting the modifiability of endogenous risk factors.

More challenging is integrating information on the non-intrinsic effects of complex endogenous processes like 'ageing', inflammation, and obesity on cancer risk that are influenced by exogenous (environment) and hereditary (genetic) as an endogenous determinant. For example, obesity has a genetic basis but most often develops as a phenotype from interaction with exogenous factors (over consumption of food and sedentary behaviour) and is thus, highly modifiable. Obesity-associated changes in metabolism, hormones and inflammation are the suspect proximate biological culprits in cancer risk and they are modifiable (metformin, anti-inflammatory drugs, lipid lowering drugs, hormone therapies). Deregulated sex hormones for example are causally linked to the significant increase risk of uterine cancer in obese women[85]. And unlike other cancers, endometrial cancer incidence has continued to increase worldwide[86] and in parallel with the obesity epidemic[87]. Notable is the reduction (modifiability) of endometrial cancer risk in the obese with weight loss surgery[88], hysterectomy or use of progestins that oppose oestrogen effects on the endometrial lining[87,88]. In contrast to endometrial cancer, the mechanophysical effects of obesity (i.e., extrinsic gastric compression) in combination with endogenous bile acid reflux into the oesophagus and resultant metaplastic response of the epithelium, explain the rapid rise in oesophageal cancer in the obese—a cancer that was exceedingly rare until the obesity epidemic, and therefore it may be highly preventable.

Here we consider a few such complex endogenous factors and their modifiability. This includes considering ageing as a decline in endogenous anti-cancer processes.

Inflammation and cancer. From the observations of Virchow and the carcinogenesis studies of Yamagiwa and Ichikawa, an 'irritation theory' of cancer was conceived where inflammation was subsequently identified as a major, and in some cancers e.g., asbestos-related mesothelioma and infection-related tumorigenesis, necessary component of malignancy[89–91]. Over the latter half of the 20th century, numerous cellular and molecular mechanism linking inflammation to malignant cell persistence and invasion have been characterized. These range from inflammation-induced reactive oxygen species that act in DNA damage and tumour initiation as well as inflammation-derived cytokine and chemokine effects on tumour growth, angiogenesis and tumour cell migration and invasion[91,92]. Most recently is the appreciation that immune cells play a significant role in suppressing anti-tumour immunity enabling tumour cell persistence and progression to life-threatening disease[93].

Such effects, and the large body of evidence from animal and human studies, have led to the inclusion of inflammation as an enabling factor to carcinogenesis[94], where inflammation is accepted to act across the continuum of tumorigenesis in a number of cancer types. The significance of inflammation in cancer development has been demonstrated in the chemoprevention field where randomized clinical trials and population studies of anti-inflammatory agents such as aspirin and other non-steroidal anti-inflammatory drugs have demonstrated the cancer prevention effects of suppressing pro-inflammatory mediators like prostaglandin E2 for several cancers[95]. Indeed, in 2015 the US Prevention Services Task Force recommended in favour of low dose aspirin use for the prevention of colorectal cancer in individuals at elevated risk that include patients with Hereditary Non-Polyposis Colorectal Cancer (HNPCC) Syndrome who carry germline mutations in mismatch repair genes[96].

While it is clear that inflammation is critical for tumour development, incorporation of inflammation in mathematical models of tumour development is lacking. This stems in part from the lack of valid biomarkers of cancer associated inflammation. As with mutational signatures of carcinogens, and more recent efforts to assess ageing, integration of inflammatory signals with the genomic and sequence data may offer insights on the magnitude of cancer burden that can be attributed to inflammation—work that would greatly enhance efforts aimed at modifying inflammation as a prevention strategy for reducing cancer incidence in the population.

Ageing. Ageing is considered among the most significant risk factors for cancer[97]. Yet, it is important to recognize that ageing can be defined chronologically or biologically. Chronological ageing contributes toward cancer by providing time for intrinsic risk as well as for exogenous and endogenous factors including mutagens to exert their effects. In contrast, biological ageing processes are more difficult to define or quantify since their full spectrum is not fully understood. The strong positive association of ageing with cancer is widely believed to reflect generalized declines in cellular and molecular system functions as an endogenous risk. Ageing encompasses at least nine recently proposed hallmarks[98] for which there are numerous overlaps to the cancer hallmarks[94]: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication.

In an effort to assess the impact of ageing, Podolskiy et al.[99] reported that accumulation of age-associated CT and GA mutations at CpG sites (common replication errors) appears to accelerate in a monotonic fashion until later in life (50–80 years) when the rate declines. The group reports that that the acceleration in mutation burden is higher in men and initiates earlier in life in men. This parallels higher overall cancer incidence in men and an earlier age (about 10 years) at which cancer incidence begins to rise in men. The authors suggest that the strong representation of age-associated mutations in tumours reflect decreases in organismal fitness with ageing that differ by gender and tissue type.

Not all biological ageing is pro-tumorigenic. For example, mechanistic studies have suggested that cell senescence and stem cell exhaustion that accelerate with ageing may explain the observed decline in incidence of cancer at the extremes of human age[100,101]. It is worth mentioning that the rate and peak timing of age-related cancer risk varies from cancer to cancer and even within subgroups of specific cancers. This suggests that there is not always a positive relationship between age and cancer risk. For breast cancers, triple negative and HER2 positive breast cancers peak earlier in adulthood and exhibit a decline with advancing age where oestrogen receptor positive breast cancer incidence rises later and continues to increase with age[102]. These results may also reflect differences in susceptible cell populations in tissues that senescence at different life-stages; life cycle biology not currently considered in modern models of cancer risk.

To tease out ageing effects on cancer from non-intrinsic risk factors is challenging. The effect of ageing on cancer risk is commonly removed by testing the cancer risk in individuals with and without the exposure matched on age. Analysis of age-adjusted incidence rates provides the most common way to address this issue. In the geographic comparisons discussed previously, all the incidence rates are age-adjusted. In these cases, the chronologic age effect is accounted for.

Heritable factors. Hereditary cancer can also operate through intrinsic and non-intrinsic mechanisms, by modulating the frequency of mutations per se (or their repair) but also by non-

intrinsic mechanisms. For example, for cancers of the breast, prostate and colon, upwards of 30–40% of the attributable risk of these cancers is thought to be due to genetic causes. A landmark paper published in 2000 of 11 cancer types in 44,788 twin pairs concluded in favour of the environment as an "overwhelming contributor to the causation of cancer", a statement that, like current discussions, prompted vigorous debates[103]. Importantly however, the work provided evidence of significant heritability in the common cancers of prostate (42%), colorectum (35%) and breast (27%). In a recent study of 80,309 monozygotic and 123,382 same-sex dizygotic twins of the Nordic Twin Study of Cancer (NorTwinCan)[104], a 33% excess familial risk was observed for all cancer with confirmation that the magnitude of excess heritable risk was cancer specific with nearly 60% of prostate cancer estimated to be influenced by genetic factors. While much of the genetic basis of cancer risk remains to be identified, it is notable that a majority of the hereditary cancer mutations as well as the germ line variants identified involve DNA repair genes thought to act by increasing mutation rates often in tissue-specific fashion. However, it is also important to note that the increased risk may also derive from genetic mechanisms resulting in increased susceptibility to non-intrinsic factors and exposures to other DNA damaging processes.

Tumour epigenetics. Our ability to understand and to model cancer aetiology and the impacts of exogenous and endogenous factors in risk has in recent years been extended to include consideration of effects of numerous factors on the epigenome. As with replication errors, epigenetic changes (e.g., DNA methylation) are passed on to daughter cells as non-sequence based chemical changes to the DNA. There is convincing evidence that epigenetic changes not only occur during tumour development, but they also play a direct causal role. This includes reproducible evidence that specific epigenetic silencing events, such as silencing of MLH-1 in a subset of human colon cancers, are essential alterations in human tumorigenesis[105]. Key epigenetics mechanisms in human carcinogenesis are beyond the scope of this perspective but have recently been reviewed for the major cancer types[106]. Noteworthy here for future models aimed at (1) identifying cancer risk factors and (2) for estimating contribution of factors (endogenous or exogenous) that impact the epigenome in cancer risk is consideration of the recent elegant work from the Baylin laboratory[107]. In their studies, they provide evidence that cigarette smoke (as a chronic exposure) induces time dependent alterations in the human bronchial epithelial cell epigenome that enhances their sensitivity to transform with a single KRAS mutation[107]. These data strongly suggest that a chronic exposure like smoking (or obesity, nutrient deprivation, ageing epigenetic effects on immune cell function, inflammation) may act by lowering the threshold of a cell to intrinsic errors for cancer development; an important interaction of the effects of the intrinsic and non-intrinsic risk factors not adequately considered in previous models. Similar effects of other exogenous and endogenous factors to the epigenome including inflammation, obesity and ageing may similarly alter the thresholds to transformation via effects on the epigenome[108,109]. Importantly, whether epigenetic changes represent reversible processes is currently debated and a subject of investigation. Studies in smokers, however, demonstrate smoking-specific changes to the epigenome persist for many years after smoking cessation, which may explain the long-lasting nature of elevated risk in former smokers.

Other endogenous factors. In addition, less well defined 'endogenous' factors such as complex gene × gene interactions and gene × environment trait interactions are increasingly recognized as 'cancer risks'. These include height and telomere length as examples along with emerging interest in the human microbiome as a modifier of cancer risk. Given progress toward understanding the significance of complex interactions in cancer, estimating their contribution to cancer burden will be important. While beyond the scope of this review, two recent lines of work on telomere genetics and cancer risk and human height and cancer risk are worth mentioning[110].

The Telomeres Mendelian Randomization Collaboration Group[110] recently demonstrated an association between genetic polymorphisms, telomere length and cancer. Longer telomere associated gene variants were associated with rare cancers and strikingly, with cancers in tissues with low stem cell divisions. As noted by the authors, the positive association with telomere length is consistent with evidence that telomere shortening with aging may act as an intrinsic protective mechanism against cancer by limiting cell division, explaining the lower rates of cancer in extreme age. While telomere length is a heritable trait, recent evidence from experimental models suggests that telomere length is malleable and influenced by numerous external stimuli[111]. Such findings provide new biological rationale for positive associations between environmental and psychosocial factors and telomere length observed in human studies that may impact cancer risk[112].

Similarly, the repeated observation between adult height and cancer risk[113] including breast[114], prostate and colon[115] is intriguing given the average height of humans continues to increase worldwide. Height is a heritable trait with estimates from twin studies suggesting that as much as 80% of height, especially in adolescence, can be attributed to parental height[116]. As such, the positive association between height and cancers has been hypothesized to reflect genetic traits that influence gestational, childhood and adolescent growth processes that also act on cancer progenitor cells. Indeed, 168 genetic variants associated with height and Mendelian randomization analysis were reported associated with genetically predicted height and risk of oestrogen receptor positive breast cancer[114]. Confounding the interpretation of these associations though is the strong influence of maternal nutrition as an equally strong non-genetic determinant of height[117]. Such important gene × environment interactions may partly explain geographical differences in risk of certain cancers like prostate cancer. For example, prostate cancer has been shown to be positively associated with height at 13 years of age[118]; a time when early life nutrition is most important in determining stature. This association was independent of adult height, suggesting nutrition in early life may be a modifying factor in prostate cancer risk. Like emerging evidence that obesity and other growth factor affect cancer risk via expansion on tissue stem cells[119], it is plausible that nutrition and height genes interact with effects on stem cells affecting an intrinsic risk factor for cancer at the tissue level. Understanding such effects will be essential for modelling the contribution of each to cancer risk. Unfortunately, integration of early life exposures including nutritional status in human studies are challenging and make it difficult to tease out the effects of early life nutrition on adult cancer[120]. Studies in animals and in birth to death cohorts, where detailed early life exposures are collected, will be critical to advancing our understanding of such factors in risk of cancer in adults[121].

Conclusions and perspective

Multiple approaches have been applied over the past few decades to understand and determine cancer exposures and risks (Boxes 1–2). These have aided in mathematical modelling approaches aimed at estimating the contributions of non-intrinsic and intrinsic factors to cancer risk and cancer burden in the

population. Overall, except for a few isolated studies[7,8], for most cancers, estimates from various approaches attribute a sizable fraction of cancer risk (60–90%) to non-intrinsic risk (Fig. 4). These estimates of non-intrinsic risk are consistent across studies and support a substantial contribution of potentially modifiable or actionable risk to cancer[77,78,122]. Evolving theories in cancer molecular pathogenesis and technological innovations (for example the deeper understanding of the cancer epigenetics mechanisms) are resulting in finer estimates of the impact of intrinsic and non-intrinsic processes based on biological principles. The rapid advances in the molecular biology of human cancers, including emergent role of stem cells in cancer evolution and expansion of long lived clones with multiple mutations and epigenetic changes, favour a much more complex picture of cancer aetiology with heterogeneity among the cancers and within cancers of the same tissue type. These pave the way for development of new analytic approaches that better integrate new knowledge including considering contributions of individual factors as well as their joint effects on cancer burden.

Much discussion has been made recently of the role of 'bad luck' in cancer risk, where the contribution of intrinsic factors to cancer is considered unmodifiable bad luck[7,8]. Thus, someone who never smoked may still have a lifetime risk of lung cancer of 0.2% to 1%. However, it is important to realize that (1) Non-intrinsic factors themselves only impart an increase in risk in developing cancer, and therefore there is still an element of luck for non-intrinsic factors. For example, whether a smoker develops lung cancer or not, an event that has a lifetime probability of 10–25%, depends on other factors including their sex and degree of smoking. Smoking increases the probability by 10 to 25 folds. Thus, exposure to risk factors does not necessitate the development of cancer; nor does the absence of exposure (with a few exceptions e.g., HPV) provide a 100% guarantee to prevent cancer. (2) Non-intrinsic and intrinsic risk factors often do not act independently as we have highlighted, and the most likely scenario is that they cooperate to cause cancer. In this regard, cancer risk can still be modified even when intrinsic factors contribute to some of the risk. As such, for some cancers there is evidence that there is an 'unmodifiable' variation arising from the built-in randomness of intrinsic and non-intrinsic mechanisms and this is likely greater in tissues with a higher level of cell division.

As such, it is detrimental to prevention and cancer control measures if the risk, especially for clinically significant cancers, is over interpreted to be due solely to bad luck. This underestimates the potential impact of prevention and control measures aimed at reducing or delaying incidence and death due to cancer. Similarly, under-estimating the fraction of preventable cancer risk impedes progress to identify modifiable exposures for cancer prevention and control measures when possible (Fig. 2).

Indeed, the proportion of currently preventable cancers is mostly a subset of cancers with known non-intrinsic risk factors (as shown in Fig. 2). Per the Cancer Research UK, ~40% of cancer burden is currently preventable. For example, at present, several cancers (e.g., prostate, thyroid, brain and testicular cancers) show no benefit from the modification of 14 lifestyle and environmental risk factors[123] even though epidemiologic and other studies suggest strong effects of the environment. Therefore, this does not negate the significant contribution of currently unidentified risk factors or that they would become modifiable. Moreover, other known non-intrinsic risk factors such as radon for lung cancer and geographic variations for breast, colorectal and prostate cancers are not currently considered in the Cancer Research UK estimates. While plausible, challenges remain in ascertaining exposure of humans to putative non-intrinsic risks with hypothesized but equivocal evidence for several suspects, including heavy metals, endocrine disruptors, cadmium, sleep deprivation, chemical mixtures especially at low doses and nutrient deficiencies (folate, selenium) identified from experimental systems as pro-tumorigenic.

Potential interactions among various risk factors further complicates measurement issues, though the identification of

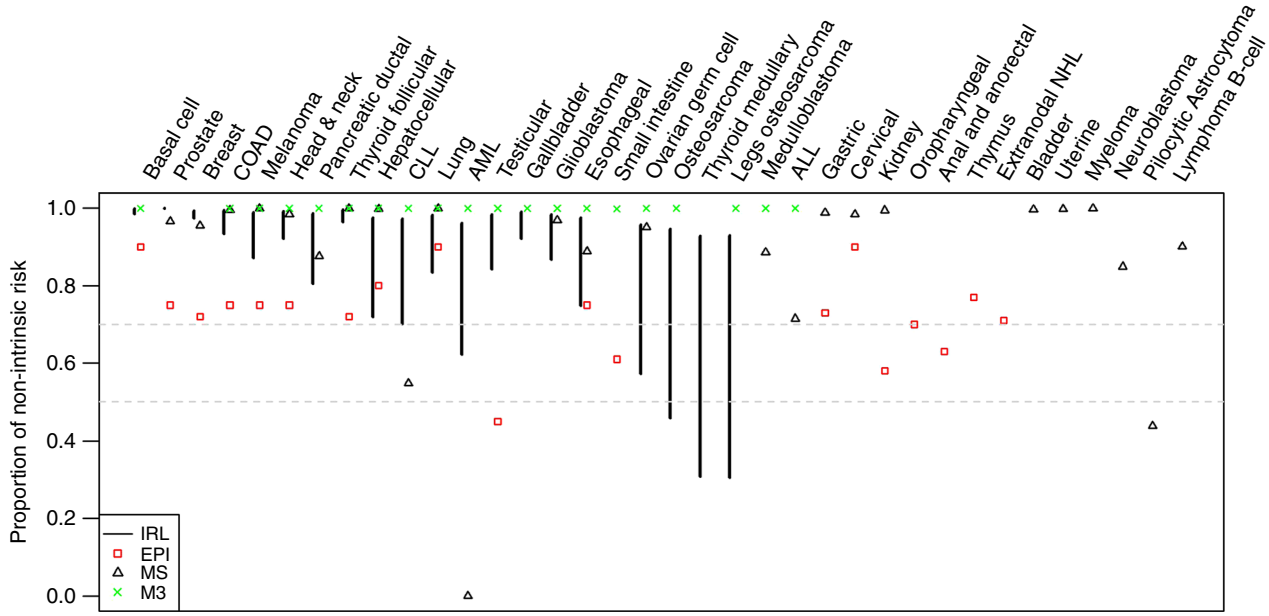

Fig. 4 Proportion of non-intrinsic risk estimates from four different approaches. Data were obtained from ref [15]. The two dashed horizontal lines indicate non-intrinsic risk at the levels of 0.5 and 0.7. IRL confidence interval from the intrinsic risk line method, EPI epidemiological estimates, MS estimates based on mutational signatures (Box 1), M3 estimates from the 3-hit model, AML: Acute Myeloid Leukemia, ALL: Acute Lymphocytic Leukemia, CLL: Chronic Lymphocytic Leukemia, NHL: Non-Hodgkin's Lymphoma. Most cancers show substantial non-intrinsic risks, except for AML, ALL, CLL and Pilocytic Astrocytoma, all of which are rare cancers and contribute less than 1% of the total cancer burden, and therefore those results do not affect our overall estimates. Moreover, AML, ALL and CLL are blood cancers whose pathogenesis and requirement for mutations may differ from solid tumours

additional modifiable risk factor(s) will likely open new venues for prevention (or at least intervention). This has been amply illustrated with the successive discovery of risk factors such as smoking, HPV, inflammation in colon cancer, and many others. With modern knowledge, there are also prevention successes in several hereditary cancers. For example, knowledge of the effects of BRCA1 mutation (an endogenous risk) on biological process has facilitated primary prevention including removal of the ovaries to reduce risk of breast cancer and benefits of tamoxifen; findings that support hormone modifying effects on endogenous risk that are modifiable. Similar concepts for the effects of aspirin in families with Hereditary Non-Polyposis Syndrome, a mismatch repair gene deficiency that increases mutation rates are likely to advance prevention efforts aimed at modifying intrinsic and other endogenous processes like ageing.

From our perspective, critical challenges going forward in understanding cancer risks include the need to continue to advance the biological understanding of cancer causation. Importantly, this includes the modern challenge of defining and distinguishing significant cancers (i.e., those that pose risk to life and significantly impact patient well-being) from those that do not and determining to what degree the attributable risk is preventable. Moving forward we need to establish comprehensive sequencing databases on both high and low-incidence regions for major cancers, and link biological theories with observed/experimental data through enhanced modelling and analysis efforts with more concerted efforts to advance models that deal with the complexity of cancer aetiology including simulating the joint effects of intrinsic and non-intrinsic risk factors.

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Author contribution

S.W., W.Z. and Y.A.H. conceived the study. S.W., W.Z., P.T. and Y.A.H. performed the literature review and wrote the manuscript. Y.A.H. and W.Z. directed the study.

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Exhibit 124

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Ovarian Cancer: Etiology, Risk Factors, and Epidemiology

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Abstract: Little is known regarding the early aspects of ovarian carcinogenesis. As a consequence, the identification of women at risk for the disease is based primarily on clinical grounds, with family history being the most important risk factor. In this review, we will discuss the various hypotheses regarding ovarian etiology and pathogenesis. In addition, we will discuss the epidemiology of ovarian cancer, including hereditary, reproductive, hormonal, inflammatory, dietary, surgical, and geographic factors that influence ovarian cancer risk.
Key words: ovarian cancer, epidemiology, risk factors, etiology, pathogenesis

Introduction

Epithelial ovarian cancer remains a highly lethal malignancy. It is the fourth to fifth leading cause of cancer deaths among women in the United States and causes more than 140,000 deaths annually in women worldwide. Despite intensive research efforts over the past decade directed toward improved detection and treatment of ovarian cancer, the majority of women diagnosed with ovarian cancer succumb to the disease. Progress in the fight against ovarian cancer has been hampered by a number of factors. These include late diagnosis, the absence of highly curative chemotherapy, and a high degree of molecular heterogeneity in ovarian tumors, a finding that is a direct consequence of the large tumor burden typical in most patients at the time of presentation. Despite the challenges, substantial progress has been made in our understanding of ovarian cancer biology, the potential mechanisms underlying protective factors, and our ability to identify women at increased risk of the disease. This is translating into more effective methods of prevention and treatment, and a corresponding fall in ovarian cancer incidence and mortality rates.[1]

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Etiology

Because of the intra-abdominal location of the ovary as well as the preponderance

of advanced disease at presentation typical of most ovarian cancers, it has been difficult to characterize changes in the ovarian surface epithelium (OSE) consistent with intraepithelial neoplasia.[2] Thus, little is known regarding the very early molecular and genetic events associated with ovarian carcinogenesis. As a consequence, the etiology of ovarian cancer remains poorly understood, and even the cell of origin of epithelial ovarian cancer has not been conclusively defined. A common but unproven hypothesis is that ovarian cancers arise in OSE cell-lined inclusion cysts, which are nests of OSE that are entrapped in the ovarian stroma, and subjected to the stimulative influence of stromal growth factors. Evidence to support the OSE as the source of ovarian cancer includes: (1) the finding of activation of cancer preventive molecular pathways specifically in the OSE by the oral contraceptive pill (OCP), a known ovarian cancer preventive[3,4]; (2) description of premalignant, dysplastic changes in the OSE using classic pathologic criteria[5]; (3) colocalization of dysplastic histologic changes with either loss of tumor suppressor activity or overexpression of cyclooxygenase 2 in the OSE of high-risk ovaries[6,7]; and (4) the finding of a transition in some early ovarian cancers from a nonmalignant to malignant OSE.[8]

Recently, an alternative hypothesis has been proposed, which suggests that the cell of origin for ovarian cancer may involve cells that have originated in the fallopian tube.[9–13] This hypothesis is speculative, but supported by the finding that most ovarian cancers have a histology similar to that of the fallopian tube. In addition, fallopian tube cancer risk is markedly elevated in women with BRCA-related hereditary risk of ovarian cancer, and an unusually high incidence of histologic and molecular signatures associated with dysplasia have been identified in the fimbriated end of the fallopian tube in prophylactic oophorectomy specimens from women at high risk.[13,14] Further, careful examination of the fallopian tube in women with serous pelvic carcinoma has demonstrated a high incidence of endosalpinx involvement, or of coexistent tubal carcinomas, with similar alterations in p53 noted in the pelvic and fallopian tube lesions, suggesting that the lesions might be genetically related.[15,16] An unusually high incidence of p53 signatures has been noted even in the fimbriated ends of fallopian tubes removed for noncancerous indications in women at presumed population-based risk of ovarian cancer.[17] It is possible that the fimbriated end of the fallopian tube may be susceptible to neoplasia when exposed to dysplastic cells shed from the OSE or even in response to ovarian stromal factors released during ovulation.

PATHOGENESIS

It has been commonly believed that ovulation, with its associated disruption and subsequent repair of the ovarian epithelium, can lead to the acquisition of genetic damage in ovarian epithelial cells and, in turn, to ovarian cancer in susceptible individuals.[18–20] The ''incessant ovulation'' hypothesis for ovarian cancer is supported by a large volume of epidemiologic evidence linking ovulation with ovarian cancer risk[18,21–29] and by the finding that spontaneous ovarian cancers arise frequently in poultry hens, which ovulate daily.[30] Of note, alterations in p53 are common in epithelial ovarian cancer. In addition, in human as well as chicken ovarian adenocarcinomas, the incidence of p53 alterations correlates with the number of lifetime ovulatory events.[31] It is possible that ovulatory events predispose the ovarian epithelium to alterations in p53, leading to defective repair of DNA and thus ovarian cancer susceptibility. The mechanism(s) by which these changes could potentially lead to neoplastic transformation of the fallopian tube is unclear.

Under the incessant ovulation model, reproductive and hormonal factors such as OCP use and pregnancy have been presumed to alter ovarian cancer risk mainly through their inhibitory impact on ovulation. Although this hypothesis is attractive, it fails to explain completely the marked reduction in the degree of ovarian cancer risk associated with factors such as pregnancy and OCP use. For example, both of these factors confer a degree of ovarian cancer protection that is much greater than what would be expected simply based on the number of ovulatory cycles that are inhibited.[21,23] In addition, pregnancy is associated with a reduced risk of ovarian cancer even in women who are known to have ovulatory dysfunction and for whom the pregnant state has little impact on the number of lifetime ovulatory cycles.[32] Further, some studies have reported a relationship between increasing risk of epithelial ovarian cancer and increasing time since last birth.[33,34] These data support the hypothesis that reproductive and or hormonal factors impact ovarian cancer risk through additional biological mechanisms unrelated to ovulation inhibition.[35] Indeed, in addition to incessant ovulation, there is evidence in support of alternative hypotheses that have been proposed to explain ovarian cancer pathogenesis, including (1) the gonadotropin hypothesis, which purports that circulating gonadotropins stimulate the ovarian epithelium and promote neoplastic transformation,[36] (2) the hormonal hypothesis which suggests that reproductive hormones can interact directly with the ovarian epithelium to promote (estrogens and androgens) or protect against (progestins) carcinogenesis,[3,4,37] and (3) the inflammation hypothesis which argues that inflammatory mediators released either during ovulation or concomitant with disease processes such as endometriosis can damage the epithelium in the ovary and or fallopian tube.[38,39] Although none of these hypotheses can fully explain all ovarian cancers, it is likely that they all play a role, and that ovarian cancer pathogenesis is a multifactorial process, involving a complex interplay of biological events related to ovulation, inflammation, and gonadal/hormonal factors.

Risk Factors and Epidemiology

As a consequence of the fact that most ovarian cancers present in an advanced stage, the molecular or tissue biomarker changes associated with the very early aspects of ovarian epithelial carcinogenesis are not well known. Moreover, even if tissue biomarker changes predictive of neoplastic transformation of the OSE were known, the relative inaccessibility of the ovary would make it difficult to use this knowledge clinically to identify women at increased risk of the disease. In addition, despite extensive serum biomarker research, there is still a lack of robust serum biomarkers that can be used reliably to identify, in a timely way, the majority of women who are destined to develop ovarian cancer.[40] Thus, in contrast to other cancers such as that of the colon or cervix, there is insufficient tissue or other biomarker information to allow clinicians to identify women at risk, and risk identification is based primarily on epidemiologic factors (Table 1).

HEREDITARY

One of the most consistent and significant risk factors for ovarian cancer is a family history of ovarian cancer, particularly in first-degree relatives.[41,42] Schildkraut et al[43] examined the family histories of ovarian cases and controls who had been identified in conjunction with the Cancer and Steroid Hormone (CASH) Study in the early 1980s. The risks of ovarian cancer in first-degree and second-degree relatives of women with ovarian cancer were found to be increased 3.6- and 2.9-fold, respectively,

TABLE 1. Risk Factors for Epithelial Ovarian Cancer

Increased	Decreased	Indeterminate
Hereditary	Reproductive	Fertility drugs
Family history of ovarian cancer	Multiparity	Exercise
Personal history of breast cancer	Breastfeeding	Cigarette smoking
Alteration in BRCA1 or BRCA2	Hormonal	
Lynch syndrome	Oral contraceptives	
	Progestins	
Reproductive	Surgery	
Advanced age	Hysterectomy	
Nulligravity	Tubal ligation	
Infertility		
Hormonal		
Early age at menarche		
Late age at natural menopause		
Hormone replacement therapy		
Estrogen		
Androgens		
Inflammatory		
Perineal talc exposure		
Endometriosis		
Pelvic inflammatory disease		
Lifestyle		
Obesity		
Geography		
Extremes in latitude		

compared with women with no family history of ovarian cancer. Analysis of the CASH data also revealed that a family history of either breast or ovarian cancer increased the risk of both cancers in first-degree relatives.[43–45] The discovery of the *BRCA1* and *BRCA2* cancer susceptibility genes confirmed the hypothesis that a fraction of ovarian cancers arise in women with a genetic predisposition. It is now thought that about 10% to 12% of women with ovarian cancer carry germline mutations in the *BRCA1* or *BRCA2* genes.[46–50] An additional 2% to 3% are from families with hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch syndrome. These families carry mutations in DNA repair genes and have as high as 10% to 13% lifetime risk of ovarian cancer, although colorectal, gastric, and endometrial cancers are more commonly seen.[51,52] Even among families with identical *BRCA1* or *BRCA2* mutations, there is heterogeneity with respect to the fraction of breast versus ovarian cancer that manifest and the age at onset. This suggests that genetic susceptibility is modified by other genetic or environmental factors. Cardinal features of hereditary cancer risk include a familial pattern suggestive of autosomal dominant inheritance, early onset, an excess of bilaterality (breast), multiple primaries (breast-ovary), and in the case of Lynch syndrome, an excess of cancers of the gastrointestinal and genitourinary tracts. Women with a familial pattern consistent with a significant risk of ovarian cancer should be referred for counseling and consideration of genetic testing (Table 2).[53]

BRCA

Families with *BRCA1* and *BRCA2* mutations represent the formerly separate syndromes of site-specific familial ovarian cancer and heredity breast/ovarian

TABLE 2. Factors Suggestive of an Inherited Predisposition to Breast and/or Ovarian Cancer for Whom Referral for Genetic Evaluation Should Be Considered

*BRCA**
Personal history of both breast and ovarian cancer
Personal history of ovarian cancer and a close relative with breast cancer at ≤ 50 y or ovarian cancer at any age
History of ovarian cancer at any age combined with Ashkenazi Jewish ancestry
History of breast cancer at ≤ 50 y and a close relative with ovarian or male breast cancer at any age
Women of Ashkenazi Jewish ancestry and breast cancer at ≤ 40 y
Women with a first-degree or second-degree relative with a known *BRCA1* or *BRCA2* mutation
Women with bilateral breast cancer (particularly if the first cancer was at ≤ 50 y)
Women with breast cancer at ≤ 50 y and a close relative with breast cancer at ≤ 50 y
Women of Ashkenazi Jewish ancestry with breast cancer at ≤ 50 y
Women with breast or ovarian cancer at any age and 2 or more close relatives with breast cancer at any age (particularly if at least 1 breast cancer was at ≤ 50 y)
Lynch
Women with endometrial or colorectal cancer who have
At least 3 relatives with a Lynch/HNPCC-associated cancer (colorectal cancer, cancer of the endometrium, small bowel, ureter, or renal pelvis) in 1 lineage
One affected individual should be a first-degree relative of the other 2
At least 2 successive generations should be affected
At least 1 HNPCC-associated cancer should be diagnosed before age 50
Women with synchronous or metachronous endometrial and colorectal cancer with the first cancer diagnosed before age 50

*Peritoneal and fallopian tube cancer should be considered as part of the spectrum of the hereditary breast/ovarian cancer syndrome.

HNPCC indicates hereditary nonpolyposis colorectal cancer.

Adapted from Schorge et al.[53] [Close relative is defined as a first, second, or third degree relative (ie, mother, sister, daughter, aunt, niece, grandmother, granddaughter, first cousin, great grandmother, great aunt)].

cancer.[54] Two thirds of these cancers are associated with alterations in *BRCA1* and the other third with alterations in *BRCA2*. The *BRCA* genes are tumor suppressor genes that play a role in the maintenance of genome integrity; they are involved in repair of double-strand DNA breaks, control of cell cycle checkpoint responses, and chromosomal segregation.[55] Affected individuals inherit an altered allele as well as normal wild-type allele for the *BRCA* genes. Loss of the wild-type alleles through either loss of heterozygosity or other somatic mutations in individuals with germline mutations in *BRCA1* and *BRCA2* leads to increases in genomic instability and tumorigenesis.[55]

The lifetime ovarian and breast cancer risks for women with *BRCA* mutations greatly surpasses that in the general population. Individuals from high-risk families with *BRCA1* mutations have an 87% cumulative risk of breast cancer by the age of 70. The lifetime risk of ovarian cancer in *BRCA1* mutation carriers is approximately 30% overall, but has been estimated to be as high as 44% in high-penetrance families.[56] The risk for breast and ovarian cancer is lower in women with mutations in *BRCA2*, with a 27% lifetime risk of ovarian cancer and an 84% risk of breast cancer.[57] Only a proportion of the women who carry *BRCA1* and *BRCA2* mutations develop ovarian cancer; the incomplete penetrance is thought to be due to multiple factors including the specific type and or location of the mutation, the status of modifying genes, epigenetic phenomena, and gene-environment interactions.[58,59] Of note, the estimated frequency of *BRCA* mutations in the general population is relatively low (1 in 300 to 1 in 800 individuals in the United States), but is considerably higher in those of Ashkenazi Jewish heritage (1 in 50).[60] Thus, in women with breast or ovarian cancer, those of Ashkenazi Jewish heritage are significantly more likely to harbor an alteration in *BRCA1* or *BRCA2*.

Lynch Syndrome (HNPCC)

A strong family history of early onset colon or endometrial cancer, or multiple malignancies of the gastrointestinal and genitourinary system should alert clinicians to the possibility of Lynch syndrome.[53] In addition to a significant lifetime risk of developing colon cancer, HNPCC patients have an increased risk of ovarian (12%) and endometrial cancers (40% to 60%).[61] These patients carry a mutation in the DNA mismatch repair genes MSH2, MLH1, PMS1, and PMS2, leading to genomic instability and cancer risk.[62] Similar to *BRCA*-related cancers, it has been observed that women with Lynch syndrome develop ovarian cancer at a younger age than women with sporadic ovarian cancer, with a mean age of 48. In half of the cases, ovarian and or endometrial cancers occur as many as 5 or more years before the onset of colon cancer, thereby being the sentinel event alerting clinicians to the possible risk of HNPCC.[63] Patients who have developed malignancies suspicious for Lynch syndrome often undergo genetic assessment in a stepwise fashion starting with screening of tumor (uterus or colon) for mismatch repair defects.[53] Patients with abnormalities on immunohistochemical evaluation of MLH1, MSH2, MSH6, and PMS2 protein expression or microsatellite instability will then typically undergo full sequence analysis of relevant genes as directed by immunohistochemical results.

REPRODUCTIVE

Parity

Case-control evidence has consistently shown that pregnancy lowers ovarian cancer risk. One pregnancy lowers ovarian cancer risk by as much as one third and the reduction in risk increases with each additional pregnancy.[21,23–27] The protective effect lingers for as long as 1 to 2 decades, but then wanes with increasing time since last birth.[33,34] In addition, pregnancy at a later age is more protective than pregnancy early in life. In fact, a pregnancy after the age of 35 is twice as protective against ovarian cancer as a pregnancy before the age of 25. It has been proposed that this would suggest a protective effect of pregnancy that is unrelated to effects on ovulation, and supporting the notion that pregnancy may clear premalignant or damaged cells from the ovary.[64–65] Infertility is associated with a 2-fold increased relative risk (RR) of ovarian cancer. Data on the impact of fertility drug use on risk have been inconsistent, perhaps because of the confounding influences of infertility and pregnancy on ovarian cancer risk.[66–69] Of note, similar to women who are fertile, women treated for infertility who successfully achieve a live birth benefit from a reduction in ovarian cancer risk.

OCP Use

Numerous case-control studies have shown that OCP use is associated with a decreased risk of ovarian cancer.[21,70] Three or more years of OCP use reduces the risk of developing epithelial ovarian cancer by 30% to 50%.[22,71] The association increases with the duration of use and appears to be independent of inherent ovarian cancer risk.[23,72] Furthermore, the duration of protection effect lasts for more than 10 to 20 years after the last use. These data are quite similar to the epidemiologic data related to parity, suggesting that parity and OCP use may share a common biological mechanism underlying their ovarian cancer protective effect.

Breastfeeding

Although the results of published studies are inconsistent, the weight of the published evidence suggests that breastfeeding lowers ovarian cancer risk. Danforth evaluated the impact of breastfeeding on ovarian cancer risk in a large study of 391

ovarian cancer cases and over 149,000 total participants.[73] Analysis was confined to parous women to evaluate the impact of breastfeeding independent of parity. The median duration of breastfeeding among women who breastfed was 9 months. As compared with never breastfeeding, any breastfeeding was not associated with a statistically significant reduction in ovarian cancer risk. However, among those women who breastfed for 18 months or more, a significant 34% decrease in ovarian cancer risk was noted as compared with never breastfeeding. A similar protective effect of breastfeeding was noted in a case-control study of parous women in New Hampshire, but only for women who had either breastfed all children, or the last born child.[74] No protective effect was found when the last born child was not breastfed. The authors speculated that breastfeeding may "reset pregnancy-related influences on ovarian cancer risk." In contrast, Jordan found a modest 2% reduction in ovarian cancer risk associated with breastfeeding, and no additional benefit from individual lactation episodes >12 months. In addition, the protective effect did not hold for serous borderline or mucinous subtypes, but was generally maintained for other histologic subtypes of ovarian cancer.[75]

HORMONAL

There is mounting evidence that the ovarian epithelium is a hormonally responsive target organ whose biology can be impacted strongly by the local hormonal environment. The normal ovarian epithelium expresses receptors for most members of the steroid hormone superfamily, including estrogens, progestins, retinoids, vitamin D, and androgens. In addition, the ovarian epithelium contains gonadotropin receptors and nonhormonal targets such as the cyclooxygenase pathway. There is therefore the potential for reproductive and environmental factors to have an impact on ovarian cancer risk through a direct biological interaction of hormonal and nonhormonal agents on the ovarian epithelium. Recent studies have indeed shown that reproductive hormones can have potent biological effects directly on the ovarian epithelium, thus impacting ovarian cancer risk. Progestins, for example, have been shown to induce apoptosis, one of the most important molecular pathways in vivo for the prevention of cancer and a pathway that mediates the action of many known chemopreventive agents. It has been proposed that progestin-mediated apoptotic effects may be a major mechanism underlying the ovarian cancer protective effects of OCP use and pregnancy (a high progestin state). Similarly, retinoids, vitamin D, and nonsteroidal anti-inflammatory drugs may have biological effects on the ovarian epithelium that are cancer preventive, whereas estrogens and androgens may have stimulatory effects on the ovarian epithelium, leading to an increased ovarian cancer risk.[3,4,37,76]

Gonadotropins

As early at the 1980s, Cramer proposed the gonadotropin hypothesis as a potential mechanism underlying ovarian carcinogenesis.[24] He proposed that elevated circulating levels of gonadotropins related to either the menopause or ovulatory events might stimulate the OSE and promote neoplastic transformation. The biological mechanisms underlying the gonadotropin hypothesis have not been well characterized, however, and the theory has fallen short in fully explaining the impact of hormonal and reproductive events on ovarian cancer risk. Recently, an excellent review by Choi has summarized the evidence in support of or against the gonadotropin hypothesis, and the published data have generally yielded inconsistent findings.[77] For example, although gonadotropin receptors have been shown to be expressed in the normal

ovarian epithelium and ovarian neoplasms, an association between serum levels of gonadotropins and ovarian cancer has not been conclusively established. Similarly, the known reduction in ovarian cancer risk associated with pregnancy and OCP use, conditions where gonadotropins are suppressed, supports the gonadotropin hypothesis; yet hormone replacement therapy, which also suppresses gonadotropins, is associated with an increase in ovarian cancer risk. Finally, gonadotropins have been shown to both inhibit and stimulate carcinogenesis in vitro, and animal data have been similarly inconsistent.

Progestins

The biological mechanism underlying the protective effect of OCP use has historically been presumed to be related to the inhibitory effect of OCPs on ovulation, and, in turn, to a lessening in the extent of ovulation-induced genetic damage accumulated in the OSE. Recent animal data, however, suggest that the OCP may have a profound, direct chemopreventive effect in the OSE, mediated by the progestin component. A 3-year study in primates has demonstrated that the progestin component of an OCP has a potent apoptotic effect on the ovarian epithelium, providing support for the hypothesis that OCPs may lower ovarian cancer risk through progestin induction of cancer preventive molecular pathways in the ovarian epithelium.[3,4] The apoptosis pathway is arguably one of the most important in vivo mechanisms for cancer prevention. Activation of apoptosis leads to the efficient disposal of cells that have undergone irreparable genetic damage and that are prone to neoplastic transformation.[78] It is thus a key molecular pathway for the elimination of premalignant cells in vivo. It is a biological mechanism associated with many known chemopreventive agents,[79–86] and pharmacologic agents that selectively enhance apoptosis have been shown to lower the risk of a variety of cancers in animals and in humans.[87] In addition, in both animal models of cancer as well as in humans, the efficacy of cancer preventive agents has been shown to correlate with the degree of apoptosis induced.[87–90] Conversely, mutations in the genes involved in the apoptosis pathway have been shown to be associated with enhanced cancer risk.[91] The finding that progestins activate this critical pathway in the ovarian epithelium raises the possibility that progestin-mediated apoptotic effects, and not solely ovulation inhibition as has been previously assumed, may underlie the reduction in ovarian cancer risk associated with routine OCP use and pregnancy.

A growing body of published human data is supportive of the notion that a biological effect related to progestins may be a major mechanism underlying the cancer preventive effect for both the OCP as well as pregnancy, which confers potent protection against subsequent ovarian cancer and which is associated with high serum progesterone levels:

(a) An analysis of the data from the CASH, has demonstrated that use of progestin-potent OCPs confers greater protection against ovarian cancer than use of OCPs containing weak progestin formulations.[92]
(b) Further support for progestins as ovarian cancer preventives has come from an analysis of data from the WHO by Risch, demonstrating a 60% reduction in the risk of nonmucinous ovarian cancer in women who have ever used Depo-medroxyprogesterone acetate, a progestin-only contraceptive.[37] Progestin-only contraceptives do not reliably inhibit ovulation. Thus, the 60% reduction in ovarian cancer risk from a progestin-only contraceptive is further evidence that progestins have a direct chemopreventive effect on the ovary.
(c) In addition, epidemiologic evidence has suggested that twin pregnancy may be more protective against

subsequent ovarian cancer than singleton pregnancy. Previously, it was presumed that women who have twins would be at greater risk of ovarian cancer, presumably due to an increased likelihood of more lifetime ovulatory events as compared with women who do not have twins, and the notion that increased ovulation would confer greater risk of ovarian epithelial damage. Because women with twin pregnancy have higher progesterone levels than women with singleton pregnancy, it has been proposed that the data regarding twin pregnancy are supportive of the notion of a biological effect of progesterone as conferring ovarian cancer protection, and that the effect is dose dependent.[64]

(d) Finally, pregnancy at a later age is more protective than pregnancy early in life, and pregnancy after the age of 35 is twice as protective against ovarian cancer as a pregnancy before the age of 25. It has been proposed that this would suggest a protective effect of pregnancy that is unrelated to effects on ovulation, and supporting the notion that pregnancy may clear premalignant or damaged cells from the ovary.[64,65] Reproductive factors such as pregnancy and OCP use may thus impact ovarian cancer risk not only through inhibition of ovulation, but also through a progestin-mediated chemopreventive effect that clears genetically damaged cells from the ovarian epithelium.

Estrogens

Data regarding the impact of estrogens on ovarian cancer risk are mainly derived from case-control series examining the impact of OCP use or hormone replacement therapy on ovarian cancer risk. As discussed above, use of estrogen/progestin combination OCPs has been shown to consistently lessen ovarian cancer risk.[71] Of note, however, in primates receiving OCPs, estrogens have been shown to partly abrogate the effect of progestins on chemopreventive endpoints such as apoptosis in the OSE, suggesting that estrogens may counteract the cancer preventive effect of progestins.[3,4] Published evidence in postmenopausal women would support this conclusion. Several large case-control studies suggest that estrogen replacement therapy increases ovarian cancer risk 2-fold, and that the addition of progestins to hormone replacement therapy partly neutralizes this enhanced risk.[93–97] Whether or not estrogen replacement therapy increases the risk for all ovarian cancers, or selectively promotes the development of specific histologic subtypes of ovarian cancer is unclear. For example, an increase in risk for endometrioid ovarian tumors has been reported among women who have used postmenopausal estrogen replacement.[97,98] A more recent study, however, has shown that menopausal hormone replacement use conferred an increased risk for all histologic subtypes of ovarian cancer except for mucinous, where risk was reduced.[99]

Androgens

It has been proposed that androgens may be associated with increased ovarian cancer risk, but the evidence is not conclusive.[37,100] Data in support of a link between androgens and ovarian cancer risk include: (1) androgen receptors (ARs) are expressed in the OSE, thereby providing a means by which androgens can have a direct biological effect in the organ; (2) most ovarian cancers express AR, and antiandrogens inhibit ovarian cancer growth; (3) oral contraceptives, potent ovarian cancer preventives, significantly lower ovarian androgen production; (4) ovarian cancer risk is increased in conditions such as polycystic ovary syndrome, which is associated with elevated serum androgen levels; (5) use of androgenic agents such as testosterone or danazol may increase ovarian cancer risk.[101,102] In contrast, however, increased

activity of the AR gene may inhibit ovarian carcinogenesis. In addition, a recent case-control study evaluating clinical surrogates for an androgenic milieu such as a history of polycystic ovary syndrome, acne or hirsutism failed to demonstrate that androgen excess is associated with increased ovarian cancer risk.[101] Finally, use of androgenic OCPs does not increase ovarian cancer risk as compared with nonandrogenic OCPs.[103]

INFLAMMATION

Ness was the first to propose that inflammatory factors might be involved in ovarian carcinogenesis.[104] In her comprehensive review in 1999, she noted that the incessant ovulation and gonadotropin hypotheses failed to adequately explain the enhanced risk of ovarian cancer associated with talc use, endometriosis and pelvic inflammatory disease (PID), as well as the protective effects associated with hysterectomy and tubal ligation. A growing body of evidence suggests that the ovarian epithelium and fallopian tube are exposed chronically to an inflammatory milieu related to the normal functions of ovulation and menstruation.[105] Pro-inflammatory cytokines are present in ovulatory fluid and also in menstrual effluent that comes into contact with the fallopian tube. These same cytokines are markedly elevated in epithelial ovarian cancers. In addition, inflammatory mediators are markedly increased in disease states such as endometriosis and PID. Recently, elevated serum levels of C-reactive protein have been shown to be associated with an increased subsequent risk of ovarian cancer.[106,107] In addition, in a prospective case-control study of 230 women with ovarian cancer and 432 individually matched controls nested within three prospective cohorts, prediagnostic circulating levels of inflammatory cytokines, such as the interleukins, have been shown to be elevated in women who subsequently developed ovarian cancer. These data provide more direct evidence that inflammation may be associated with ovarian cancer risk.[108] Interestingly, OCPs, which as described above, markedly lower ovarian cancer risk, confer a number of biological effects that can mitigate inflammatory influences in the genital tract, including inhibiting ovulation, lowering the risk of PID, and reversing endometriosis.[109]

Talc

Evidence demonstrating an association between talc use and an increased risk of ovarian cancer suggests that environmental toxins can enter the lower genital tract and migrate upward through the uterus and fallopian tubes to enter the peritoneal cavity and act as ovarian carcinogens. Talcum powder was first implicated in the risk of ovarian cancer in the 1960s when it was found to be biologically similar to asbestos which is a known carcinogen. Subsequent studies in animals and humans demonstrated not only that talc deposited in the gynecologic tract could reach the ovaries, but also the finding of talc particles in ovarian neoplasms.[110] Subsequent case-control studies of talc use and risk of ovarian cancer have shown a strong association, including a meta-analysis of 16 studies that included 11,933 women demonstrating a 33% increased risk of ovarian cancer.[111–115]

Endometriosis

Endometriosis has been consistently shown to be associated with an increased risk of ovarian cancer, with odds ratios of approximately two.[104,116] The underlying mechanism is not fully characterized. It has been proposed that chronic inflammation can lead to neoplastic transformation of endometriotic implants. In addition, it is possible that the endometriotic state leads to a relative progesterone "resistance", thereby mitigating the potential protective effects of the hormone.[117,118] The most common histologic subtypes of ovarian cancer associated

with endometriosis are clear cell and endometrioid carcinomas.[119]

PID

PID occurs as predominantly a consequence of sexually transmitted diseases and manifests clinically as a marked inflammatory process involving the uterus, fallopian tubes, and ovaries. Limited case-control evidence suggests an increased risk of ovarian cancer among women who have had PID.[120,121] The association appears to be most pronounced in women who have had PID at a young age, or who are infertile, which is also an ovarian risk factor. In the largest study to date, with over 67,000 women with PID and over 135,000 controls, the adjusted hazard ratio for ovarian cancer in women with PID was 1.92, increasing to 2.46 in women who had had 5 or more episodes of PID. The adjusted hazard ratio was higher for women aged 35 or younger.[121]

SURGERY

Hysterectomy and tubal ligation are associated with a reduction in the risk of developing ovarian cancer. In a meta-analysis of 12 case-control studies, hysterectomy (without oophorectomy or salpingectomy) was associated with a 34% reduction in the risk of ovarian cancer.[29] Women who underwent a tubal ligation also had a 34% risk reduction compared with women who did not.[122] The protective effect of surgery also extends to women at hereditary risk of ovarian cancer. A case-control study by the Hereditary Ovarian Cancer Clinical Study Group has shown that tubal ligation lowered the rate of ovarian cancer in women with *BRCA1* alterations by 60%.[123] The combination of tubal ligation and OCP use reduced the risk even further. Of note, no protective effect of tubal ligation was seen among carriers of the *BRCA2* mutation. The mechanism for the protective effect of tubal ligation and hysterectomy is not known, but theoretically could be explained by blockage of access of environmental carcinogens to the ovaries. Another proposed mechanism is that surgery to remove uterus or fallopian tubes may affect the ovarian circulation or plasma hormone levels in ways that lower ovarian cancer risk.[124] Finally, if the fallopian tube is indeed the source of some ovarian cancers, then removing some of the tube may be expected to lower cancer risk.

LIFESTYLE

Obesity

It is likely that obesity increases the risk of ovarian cancer, but the degree of effect is modest. A systematic review reported a small association between body mass index (BMI) >30 and ovarian cancer risk with an odds ratio of 1.3 [95% confidence interval (CI), 1.1-1.5].[125] In the Cancer Prevention Study, a prospective cohort study of 495,477 women followed for 16 years, a relationship was noted between high BMI and ovarian cancer mortality.[126] The RR of death from ovarian cancer among women with a BMI of 35 to 40 was 1.51 compared with those of normal weight. Findings from the Nurses' Health Study indicated a 2-fold increased risk of premenopausal ovarian cancer associated with a high BMI.[127] In addition, a meta-analysis showed an association between obesity and ovarian cancer with a 40% increase in risk in the heaviest versus the lightest women in population-based case-control studies.[128] A recent study by Leitzman prospectively followed 94,525 patients over a 7-year period.[129] Overall, the women with a BMI > 30 were 1.26 times more likely to have developed ovarian cancer, though those findings were not statistically significant. Among a subgroup of women who had never used hormone replacement therapy, the women who were obese were 1.83 times more likely to develop ovarian cancer. In

women who had used hormone replacement therapy, there was no association between obesity and ovarian cancer. The authors speculated that obesity is associated with enhanced ovarian cancer risk through a hormonal mechanism. Obesity is known to increase adrenal secretion of androgens, and is generally associated with an increased endogenous production of estrogens.[130]

Diet

Numerous studies have attempted to identify dietary factors that may influence ovarian cancer risk. Overall, the results have been inconsistent or conflicting. The balance of the evidence has failed to conclusively demonstrate that consumption of any macronutrient or micronutrient significantly alters ovarian cancer risk. A case-control study in Italy comparing 455 cases with ovarian cancer to 1385 age-matched controls revealed an increased RR for ovarian cancer associated with meat consumption of >7 portions versus less than 4 portions per week (RR 1.6; 95% CI, 1.2-2.12) and butter versus fat consumption (RR 1.9; 95% CI, 1.20-3.11). Dietary risk factors that decreased risk included whole-grain bread and pasta consumption.[131] A larger prospective cohort study of 29,083 women in the United States found that egg consumption of 2 to 4 times per week as well as increased intake of carbohydrates and dairy increased the RR of developing ovarian cancer, whereas consumption of green leafy vegetables significantly decreased risk (RR 0.44, 95% CI, 0.25-0.79), but there was no association with dietary fat, as well as intake of meats, breads cereals, and starches and ovarian cancer risk.[132]

Studies evaluating the intake of specific foods or food groups on the subsequent development of ovarian cancer have similarly yielded inconsistent results. In one study, protective foods included olive and vegetable oils, fish, peas, beans, and lentils.[133] Vegetable consumption was found to be protective in one study[134] but another study that examined the effect of consumption of vegetables and fruits noted no benefit.[135] In another large study, risk of ovarian cancer was studied after consumption of fruit and vegetables. There was no association found between high consumption of fruits and vegetables and ovarian cancer risk.[136] A study in 2006 suggested that milk and milk products are associated with an increased ovarian cancer risk.[137] However, the Netherlands Cohort Study on Diet and Cancer which followed 62,573 women for 11.3 years and included 252 cases with ovarian cancer found no association between lactose and dairy intakes and the development of ovarian cancer.[138]

In attempt to further clarify dietary associations with ovarian cancer risk, 2 studies evaluated general dietary patterns as opposed to specific foods. Overall diet was evaluated in the prospective California Teachers Study.[139] A total of 97,292 women completed a baseline dietary assessment of which 311 developed epithelial ovarian cancer. Five major dietary patterns were compared: (1) plant-based; (2) high protein/high fat; (3) high carbohydrate; (4) ethnic; (5) salad and wine. Although women who followed a plant-based diet had a slightly higher risk of ovarian cancer (RR 1.65, 95% CI, 1.07-2.54), the authors concluded that their results did not show convincing associations between dietary patterns and ovarian cancer risk. A recent study published in 2011 evaluated the association between a Healthy Eating Index and ovarian cancer.[140] The Healthy Eating Index reflects adherence to current USDA dietary Guideline for Americans. This population-based case-control study had a total of 205 women with ovarian cancer and 390 controls. Based on their results, the authors concluded that neither individual food groups nor dietary quality showed potential for preventing ovarian cancer.

Exercise

There is no firm relationship between exercise and ovarian cancer risk. Studies to date are small and generally inconclusive, with results ranging from suggesting no association, to a finding of a modest benefit from exercise, to even a possible adverse effect of vigorous exercise on ovarian cancer risk.[141–144] Pan et al[145] examined survey responses from over 400 women with ovarian cancer and over 2100 healthy women from The Canadian National Enhanced Cancer Surveillance System. Women who reported moderate levels of recreational physical activity or who held jobs with moderate or strenuous physical activity had a reduced risk of ovarian cancer with an odds ratio of 0.67 (0.50 to 0.88). A large study from the Netherlands Cohort Study consisting of 62,573 women who were surveyed regarding their physical activity yielded similar conclusions. Two hundred fifty-two cases of ovarian cancer were identified after 11.3 years of follow-up. Compared with women who exercised <30 minutes per day, women who spent >60 minute per day in moderate exercise had a RR of 0.78 for the development of ovarian cancer. Women who spent >2 hours per week on recreational biking and walking had an even lower risk (RR 0.65; 95% CI, 0.41-1.01) compared with women who did no exercise.[146] In contrast, in the very large Nurses Health Study, although moderate activity was found to be protective against subsequent ovarian cancer, frequent vigorous exercise was associated with increased risk.[143] The underlying mechanism(s) potentially mediating the effects of exercise on ovarian risk are not well known. Hormonal changes associated with physical activity can cause anovulation and decrease the risk of obesity thereby lowering estrogens and risk, but possibly increase gonadotropins which may increase risk.

Cigarette Smoking

The effect of smoking on ovarian cancer risk has not been well defined. The most intriguing finding has been an association between current or past smoking and an increase in mucinous ovarian cancer, although the association does not apply to other histologic subtypes.[147–151] The biological basis underlying any association between smoking and ovarian cancer is not well understood. Nicotine and its metabolites have been identified in ovarian tissue.[152] Thus, it is plausible that these agents can cause direct DNA damage in the OSE. In addition, cigarette smokers have been found to have higher circulating levels of gonadotropins and androgens, both of which can have adverse effects on risk. On the other hand, smokers may have earlier onset of menopause which would be expected to lower risk.[153–155]

GEOGRAPHY

Worldwide, there is a geographic distribution for ovarian cancer, with increasing incidence commensurate with latitudinal distance from the equator.[156] The same pattern holds in the United States where there is a significant north-south gradient, favoring a higher ovarian cancer risk in northern versus southern latitudes in the United States. Lefkowitz has correlated population-based data regarding ovarian cancer mortality in large cities across the United States with geographically based long-term sunlight data reported by the National Oceanic and Atmospheric Administration, demonstrating a statistically significant inverse correlation between regional sunlight exposure and ovarian cancer mortality risk.[157] Given that sunlight induces production of previtamin D in the skin, it is interesting to speculate that vitamin D might confer protection against ovarian cancer by direct biological effects in the nonmalignant ovarian epithelium, similar to that induced by progestins. For example through induction of apoptosis and/or transforming growth factor-β in the ovarian epithelium,

vitamin D may cause the selective removal of nonmalignant, but genetically damaged ovarian epithelial cells.[158,159] A small case-control study supports the notion that vitamin D confers ovarian cancer prevention, at dosages of vitamin D easy to achieve through the diet. As compared with a low dietary intake of vitamin D, a high dietary intake of vitamin D was associated with a 50% reduction in ovarian cancer risk.[160]

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Exhibit 125

Risk Factors for Ovarian Carcinoma

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KEYWORDS

• Ovarian cancer • Risk factors • Descriptive epidemiology • Risk reduction
• Tumor heterogeneity

KEY POINTS

- Ovarian cancer continues to be the leading gynecologic killer of women in the United States.
- Most women present with advanced-stage disease at time of diagnosis and there are currently no effective screening strategies for average-risk women.
- Cancer epidemiology greatly contributes to the understanding of factors that may modify disease development and drive tumor heterogeneity.

INTRODUCTION

Ovarian cancer is the second most common gynecologic malignancy overall worldwide and the most lethal gynecologic malignancy in the United States and Europe. Each year, approximately 200,000 women worldwide are diagnosed with ovarian cancer and approximately 125,000 women die from the disease.[1] Most patients present with advanced-stage disease because symptoms of early-stage disease may be subtle or generalized.[2] Standard treatment of advanced ovarian cancer involves cytoreductive surgery in combination with taxane-platinum–based chemotherapy.[1] However, most patients experience recurrence and eventually succumb to their disease even with optimal initial treatment.[3]

Given this, identifying risk factors, preventive strategies, and high-risk populations is crucial. However, epidemiologic studies face several challenges. First, ovarian cancer is rare. Furthermore, because ovarian cancer is a heterogeneous disease, considering

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outcomes of specific cancer subtypes is critical to provide clues to underlying mechanisms. As a result, it is crucial to have large sample sizes to ensure power. Thus, several consortia have been initiated to pool resources from multiple studies and conduct investigations that would not be possible in any single study. Pooling studies that span different time periods further allows addressing a second challenge, which is the temporal changes in clinical characterization of ovarian cancer and changes in certain exposures (eg, oral contraceptive pill [OCP] doses) over time.

Importantly, removal of the ovaries and fallopian tubes reduces risk by up to 80% to 90%.[4] However, negative health consequences, including cardiovascular mortality,[5,6] necessitate the use of this procedure only among high-risk women who would have a net benefit, such as those with *BRCA* or other high-penetrance mutations. However, in average-risk women, efforts to develop well-calibrated risk prediction models have been largely unsuccessful, with low predictive capability even when using known ovarian cancer risk factors (area under the curve [AUC], 0.59–0.64).[7–10] Addition of low-penetrance alleles only modestly improved the AUC to 0.66,[11] requiring identification of new risk factors.[12] A potential reason for the low predictive ability is ovarian cancer heterogeneity, necessitating consideration of subtype-specific risk factor associations. The focus of this article is to review risk factor associations by tumor subtypes to inform the future research that is needed to improve risk prediction.

NONEPITHELIAL OVARIAN CANCER RISK FACTORS

A small proportion of ovarian tumors are from a nonepithelial origin and generally have not been considered in risk modeling efforts. Specifically, sex-cord stromal ovarian neoplasms represent only 1.2% of ovarian cancer cases. These tumors are diagnosed at earlier stages and younger ages, in sharp contrast with epithelial ovarian cancer.[13] Limited data suggest that nonwhite, obese women with a family history of breast or ovarian cancer are at increased risk for this subtype. *BRCA* germline mutations or a genetic predisposition to breast cancer are not related,[14] although germline mutations in *DICER1*[15] and somatic mutations in *FOXL2* are related to these tumors.[16] Ovarian germ cell tumors account for 5% of malignant ovarian neoplasms,[17] with early stage at younger ages.[18] The incidence increases around puberty.[19] There is a greater incidence among Asian/Pacific Islander and Hispanic women than in white women.[20] No definite genetic abnormalities have been identified in families with germ cell tumors.

EPITHELIAL OVARIAN CANCER RISK FACTORS

Epithelial ovarian cancer comprises greater than 90% of malignant epithelial neoplasms and often is diagnosed in postmenopausal women. Incidence is higher in white women (12.8 per 100,000) than in black women (9.8 per 100,000).[21] Incidence seems to be lowest for American Indians/Alaska Natives. Incidence has been declining, with a 1.6% decrease in incidence and 2.1% decrease in mortality per year from 2003 to 2012 in the United States.[22]

Many traditional ovarian cancer risk factors are reproductive or hormonal. In general, processes that decrease the number of ovulatory cycles are protective. For example, OCP use, multiparity, breastfeeding, and tubal ligation, as well as late age at menarche and early age at menopause, have been consistently associated with decreased risk, many with a dose-response relationship.[22] However, studies among women using more recent lower-dose OCP formulations do not observe a decreased risk except with very long durations of use (>10 years).[23–25] Further, use of hormone therapy, including unopposed estrogen and combined estrogen and progestin, seems

to increase risk.[26–31] Other risk factors include endometriosis, taller height, and high body mass index in adolescence.[32–36]

Variation in Risk Associations according to Ovarian Cancer Subtypes

Ovarian cancers represent a diverse group of diseases that are unique based on precursor lesions, histology, cause, developmental origins, as well as distinct mutational profiles.[37,38] Stratification based on subtypes is critical for understanding mechanisms underlying risk factor associations and for developing improved risk prediction models. Although the most common assessment of heterogeneity is based on histologic subtypes (ie, the morphologic features of the tumor) and grade, other metrics have also been used. Large-scale studies that examined risk factors for specific ovarian cancer subtypes are summarized later.

Histologic subtypes

Unexpectedly, most known ovarian cancer risk factors show stronger associations with nonserous tumors, which comprise ~25% of epithelial ovarian cancers, than the more aggressive serous tumors (**Table 1**). For example, in a pooled analysis of 21 prospective cohort studies in the Ovarian Cancer Cohort Consortium (OC3), reproductive risk factors, including lower parity and older age at menopause, as well as endometriosis, were associated primarily with increased risks of endometrioid and clear cell tumors.[31] This finding is consistent with pooled analyses of case-control studies and studies of endogenous hormones.[39,40] Notably, OCP use seems equally protective across histologic subtypes in multiple studies.[31,39] Surgical procedures, including tubal ligation and hysterectomy, also seem to primarily decrease the risk of nonserous tumors.[31,41–44] Data on histologic subtype–specific associations for salpingectomy are currently unavailable, because few studies have examined this association and most have had few exposed cases.[31,42,43]

Associations of several lifestyle factors and use of over-the-counter medications with risk of specific ovarian cancer histologic subtypes have also been investigated. Smoking was associated with an increased risk of mucinous ovarian tumors but a decreased risk of clear cell tumors in several studies.[31,45] A pooled analysis of 8 case-control studies found modest increases in risks of serous, endometrioid, and clear cell carcinomas, but not mucinous tumors, in women who used genital talc powder.[46] Aspirin and other nonsteroidal antiinflammatory drug use was mainly associated with serous disease in both prospective and retrospective consortial analyses.[47] Similarly, history of ovarian cancer is one of the few factors that is more strongly associated with serous carcinoma.[31] Family history of breast cancer was most strongly related to endometrioid tumors.

Multiple studies have integrated grade and histologic subtype to evaluate associations for high-grade and low-grade serous tumors separately because these are thought to have different causes.[31,42,43] In general, low-grade serous tumors had similar associations to endometrioid and clear cell disease, although family history of ovarian cancer was related to high-grade serous tumors.[31] A key caveat in these studies is that grade does not have standard classification criteria and is often missing in epidemiologic studies, reducing power and leading to misclassification of disease subtype.

Biologically, these results support the theories of differing cells of origin in ovarian cancer, notably with endometriosis and tubal ligation being strongly associated with histologic subtypes thought to be directly linked with endometriotic tissue and retrograde menstruation.[48] Similarly, the family history of ovarian cancer relationship with high-grade serous disease is likely explained in part via BRCA mutations. In the

Table 1
Summary of putative cells of origin and identified risk factors for specific ovarian cancer histologic subtypes

Subtype	Putative Cells of Origin	Reproductive and Hormonal Risk Factors	Family History, Demographic, and Lifestyle Risk Factors
All serous	Ovarian surface epithelium, fallopian tube epithelium	Lower parity[31,39] Shorter duration of OC use[31,39] HT use/longer duration of use[31,39] No history of tubal ligation[42–44]	Family history of breast cancer[31] Family history of ovarian cancer[31] Taller height[31] Genital powder use[46] No regular aspirin use[47]
High-grade serous	Ovarian surface epithelium, fallopian tube epithelium	Lower parity[31] Shorter duration of OC use[31] Longer duration of HT use[31] No history of tubal ligation[42,43]	Family history of ovarian cancer[31] Taller height[31]
Low-grade serous	Ovarian surface epithelium, fallopian tube epithelium	Lower parity[31] Shorter duration of OC use[31] Longer duration of HT use[31]	—
Endometrioid	Endometriosis	[a]Lower parity[31,39] Shorter duration of OC use[31,39] HT use/longer duration of use[31,39] [a]Older age at menopause[31,39] [a]No history of tubal ligation[31,42–44] Endometriosis[31]	[a]Family history of breast cancer[31] Taller height[31] Genital powder use[46]
Clear cell	Endometriosis	[a]Lower parity[31,39] Shorter duration of OC use[31,39] Shorter duration of HT use[31] [a]Older age at menopause[31,39] [a]No history of tubal ligation[31,42,43] No history of hysterectomy[31] Endometriosis[31]	Taller height[31] Never smoking[31] Genital powder use[46]
Mucinous	Unknown	Lower parity[31,39] No history of tubal ligation[42]	Taller height[31] More pack-years[31,45]

Abbreviations: HT, postmenopausal hormone therapy; OC, oral contraceptive.
[a] Indicates that the risk factor was most strongly related to this subtype(s).

OC3 analysis, unstructured hierarchical clustering suggested that few known risk factors were associated with serous tumors compared with endometrioid and clear cell diseases, which had very similar risk factor profiles.[31] This finding is in stark contrast with breast cancer, for which risk factors for the most common type of tumor (estrogen receptor positive) are well understood, and may explain the poor predictive ability of prior risk models. Focusing on the risk factors that have been identified for serous disease may open up new areas of research to identify novel risk factors to best identify high-risk women and elucidate novel risk-reduction strategies.[49]

Type 1 versus type 2

An additional method of classifying ovarian cancer subtypes groups certain histologic subtypes together based on putative cells of origin and somatic mutations and has been used in risk factor studies to enhance power.[50] Type 1 cancers consist of low-grade serous, endometrioid, clear cell, and mucinous cancers arising from the ovarian

epithelium or endometriosis and are characterized by mutations in *KRAS*, *ARID1A*, *PIK3CA*, *PTEN*, and *BRAF*. Type 2 cancers, which comprise high-grade serous cancers, carcinosarcomas, and undifferentiated carcinomas, are characterized by *TP53* mutations and likely originate from the distal end of the fallopian tube. In general, these studies have observed similar associations to those described earlier when looking at the finer granularity of histologic subtype and grade. For example, reproductive factors such as parity and tubal ligation were most strongly associated with a lower risk of type 1 tumors, whereas OCP use was consistently associated with a lower risk across both types.[39,51,52]

Anatomic site

Research on ovarian cancer has historically encompassed primary ovarian, primary peritoneal, and primary fallopian tube cancers. However, several studies have explored whether risk factor profiles differ by the anatomic site of the cancer, which might imply different carcinogenic origins. Among these studies, most have used case-case designs in which peritoneal or fallopian tube cancer cases were compared with ovarian cancer cases,[53–57] although several studies compared 2 or more case groups defined by site of origin with a common healthy control group,[58,59] allowing direct comparison of odds ratios (ORs) across anatomic sites. Although results are not entirely clear, these studies suggest that associations of several established risk factors may vary by tumor site of origin such that associations with ovarian cancer are in the expected direction, whereas associations with fallopian tube and peritoneal cancers may be similar, null, or in the opposite direction.

For example, in the Australian Ovarian Cancer Study (AOCS), which included invasive serous ovarian (n = 627), peritoneal (n = 129), and fallopian tube cancer cases (N = 45) and 1508 control women, higher parity and longer duration of breastfeeding were each associated with lower risks of ovarian cancer; the associations with fallopian tube cancer were similar to those for ovarian cancer, whereas the associations with peritoneal cancer were null or attenuated.[59] In the North Carolina Ovarian Cancer Study (NCOCS), which enrolled 495 women with epithelial ovarian cancer, 62 women with primary peritoneal cancer, and 1086 control women, ORs for ever being pregnant and number of pregnancies were similarly inverse for ovarian and peritoneal cancers; however, older age at last pregnancy was associated with a decreased risk of ovarian cancer (OR, 0.58; 95% confidence interval [CI], 0.39–0.86 comparing age $\geq$ 35 years vs <25 years), but an increased risk of peritoneal cancer (OR, 2.78; 95% CI, 1.00–7.78). Similarly, tubal ligation was associated with reduced risk of ovarian cancer but not associated with peritoneal cancer in NCOCS, although the RRs were not statistically significantly different. In AOCS, the reduction in risk caused by tubal ligation was similar across anatomic sites.[58]

Given the limited the number of studies, it is difficult to conclude whether cancers at different anatomic sites should be considered distinct outcomes. Continued collaborative efforts are warranted in order to achieve an adequate sample size for continued investigation.

Tumor dominance and laterality

It is now accepted that a substantial proportion of serous tumors arise from the fallopian tubes, whereas some nonserous histologic subtypes, such as endometrioid, may arise from endometriosis or retrograde menstruation. Because ovarian cancer is usually diagnosed at a late stage when disease has spread, determining the cell of origin is often very difficult.[49] Pathology studies have suggested that dominant tumors (restricted to 1 ovary or at least twice as large on 1 ovary compared with the

other) are less likely to have a serous tubal intraepithelial carcinoma and are more likely to be of nonserous histologic subtypes, compared with those with tumor spread more evenly or diffusely across the peritoneal cavity. Further, endometriosis is often found on the left side; this may reflect greater ovulation events on the right side, leading to higher localized progesterone production, which suppresses endometriosis, as well as less efficient elimination of retrograde menstruation caused by anatomic proximity with the colon or decreased flow of peritoneal fluid on the left.[34] Thus, laterality of dominant tumors may be more likely to be related to this cell of origin.

Specifically, in a study of 1386 tumors, nondominant tumors were more likely to be serous and stage III/IV. In addition, nondominant tumors were associated with BRCA 1/2 mutation carrier status, higher parity, and use of estrogen hormone therapy. The association with BRCA mutations supports the now accepted theory that the distal fallopian tube is the site of high-grade serous cancers among BRCA mutation carriers.[60] In another study among 1771 patients with invasive epithelial ovarian cancer, 61% were dominant, whereas 39% were nondominant. Reproductive factors such as tubal ligation, 2 or more births, endometriosis, and age were more strongly associated with dominant tumors than nondominant tumors,[61] again supporting the role of reproductive factors in tumors with a non–fallopian tube site of origin. These large studies provide provocative evidence of different developmental pathways of ovarian tumors based on a woman's risk factor profile.[60,61]

Tumor aggressiveness

There is wide variation in length of ovarian cancer survivorship. Surveillance, Epidemiology, and End Results (SEER) data from 1998 to 2007 indicated that 47.1% of patients died of ovarian cancer within 3 years of diagnosis versus 34.1% of patients who survived longer than 10 years after diagnosis. In a combined analysis of 4 studies (2 cohort and 2 case control) with a total of 4342 ovarian cases, cases were classified as being rapidly fatal (ie, death within 3 years) or less aggressive disease (all others). Older age (positive association) and OCP use (protective association) were more strongly associated with rapidly fatal than less aggressive disease. Higher parity was only associated with a decreased risk of less aggressive disease. Results were consistent after accounting for differences in study design, geographic location, and timing across cohorts, although sparse data on tumor grade and treatment prevented rigorous consideration of these factors in analyses. Overall, these results may contribute to development of primary prevention strategies for the most aggressive cancers.[35]

GENETIC MUTATIONS AND PREDISPOSITION

Family history remains one of the strongest risk factors for epithelial ovarian cancer. Women with a first-degree relative with ovarian cancer have a 3-fold increased risk of developing the disease compared with women with no family history. Twin studies indicate that inherited genetics are more significant than environmental and lifestyle factors.[62] *BRCA1* and *BRCA2* gene mutations are high-penetrant susceptibility genes and the most influential predictors of inherited risk for ovarian cancer. About 15% of patients with high-grade serous epithelial ovarian cancer have a germline mutation in one of the *BRCA* genes.[63] Women with BRCA mutations almost exclusively develop serous histologic subtype disease.[41] Consistent with this pattern, family histories of breast and ovarian cancer were each associated with an increased risk of serous tumors in the OC3. Family history of breast cancer was also associated with endometrioid carcinomas.[31] The overall risk of ovarian cancer for a woman with a *BRCA1*

mutation is approximately 39% to 46% and 10% to 27% for *BRCA2* mutation carriers by age 70 years.[64–67] In the general population, the estimated risk of carrying a *BRCA* mutation varies between 1 in 300 and 1 in 800 individuals. However, in certain populations, such as Ashkenazi Jews, the mutations are found more frequently in about 1 in 40 individuals. Risk-reducing surgery for known *BRCA* carriers by bilateral salpingo-oophorectomy has been successful in reducing epithelial ovarian cancer mortality. Typically, surgery is recommended for *BRCA1* carriers aged 35 to 40 years and *BRCA2* carriers aged 40 to 45 years, taking into account the patient's future childbearing preferences.[41]

More recent evidence indicates that methylation of the BRCA1 promoter in white blood cells (WBCs) is an additional factor influencing ovarian cancer risk. An analysis of blood samples obtained from 1541 women with ovarian cancer before chemotherapy and 3682 matched controls found that most of the women, regardless of case-control status, had normal germline *BRCA1* test results. However, 9% of women with cancer had abnormal methylation in the *BRCA1* promoter in circulating WBCs compared with 4% of control participants. After adjusting for multiple factors, the presence of methylated *BRCA1* conferred a 3-fold higher risk of ovarian cancer. If confirmed in prospective studies, systemic abnormal promoter methylation of BRCA could be one of the strongest known risk factors beyond germline BRCA mutations.[68] Further, understanding of its relationship to different histologic subtypes of disease would also elucidate the cause of ovarian carcinogenesis.

All the known susceptibility alleles that have currently been identified account for less than half of the heritable component of ovarian cancer, suggesting there are more mutations to be discovered. Although clinical management of *BRCA* mutation carriers is clear, clinical difficulties arise when counseling patients with intermediate-risk susceptibility genes. These genes include *FANCM*, *RAD51C*, *RAD51D*, *BRIP1*, and DNA mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*). The DNA mismatch repair genes are associated with the autosomal dominant, inherited Lynch syndrome, which confers greater risk of gynecologic cancers, with endometrial cancer remaining the most common, but also an increased risk of ovarian cancer. Women with Lynch syndrome who develop ovarian cancer typically have nonserous histology with endometrioid and clear cell tumors as the most common subtypes. Epithelial ovarian cancer risk is estimated to be 4% to 20% in *MLH1* carriers, 7.5% to 20% in *MSH2* carriers, and up to 13.5% in *MSH6* carriers. *PMS2* mutations account for very few cases. Genome-wide association studies have identified 39 independent epithelial ovarian cancer risk regions, with each risk region associated with only modest increased risk. All of these alleles have been associated with high-grade serous epithelial ovarian cancer. In contrast with high-penetrant genes, most of these common variant risk alleles are located in the non–protein-coding regions of the genome, implying that epigenomic regulation of 1 or more target genes is necessary and that they are not directly involved in DNA repair.[63] However, OncoArray and the Collaborative Oncological Gene-Environment Study (OCAC) identified 30 epithelial ovarian cancer risk loci by genome-wide association studies and examined their associations with specific histologic subtypes. They found that *HOXD9* is a likely target susceptibility gene in both serous and mucinous histologic subtypes that also affects focal adhesion within a cancer-related pathway. *HNF1B* was downregulated in most serous ovarian cancers, but overexpressed in clear cell ovarian carcinomas.[69] Histologic subtype–specific studies such as this one will help further the understanding of risk reduction given the heterogeneity of ovarian cancer.

SUMMARY AND RECOMMENDATIONS

This article indicates that, although epidemiologic studies have made strides in elucidating variations in risk factor profiles according to several classifications of ovarian cancer subtypes, much work is yet to be done to yield results that will shift clinical practice. Current risk prediction models are not accurate enough to factor into decisions about preventive treatment strategies. Following are several recommended research priorities for epidemiologic studies to move closer toward clinical translation potential.

Studies focused on understanding the genetic architecture of ovarian cancer, and particularly ovarian cancer subtypes, are critical to establish effective risk-reduction models. Further, research that goes beyond germline mutations to consider methylation and other DNA modifications, as well as downstream phenomena such as RNA transcription, proteomics, and metabolomics, may be a fruitful approach to better characterizing the variable role of genetics in ovarian carcinogenesis.

In addition, to complement gains in knowledge about the genetics of ovarian cancer, an important focus of epidemiologic research is discovery of novel nongenetic risk factors, especially with regard to high-grade serous ovarian carcinoma, the most common subtype with the most aggressive behavior but the least understood risk factor profile. A more comprehensive understanding of the underlying biology linking risk factors with specific disease subtypes will be critical for developing targeted preventive interventions for women at high risk of ovarian cancer. This work has already begun, with research examining psychosocial factors, environmental exposures, and inflammation, among other factors. For example, there is evidence that C-reactive protein may be more strongly related to risk of serous than nonserous cancer.[70] However, to better elucidate these subtype-specific associations, larger consortial studies are needed and thus greater collaboration among investigators and institutions.

Further, investigators should consider whether the tumor subtype classifications discussed in this article are optimal for clustering subtypes with a common cause, or whether different approaches are warranted. It is possible that traditional disease classification using pathology, molecular characteristics, and survival metrics do not correlate well with tumor developmental biology or the risk factor profiles underlying tumor development. New research focused on investigating the multitude of tumor characteristics (eg, immune markers, microenvironment) will likely uncover new causal factors.

In addition, the ultimate goal of the research recommended here is to improve the ability to prevent ovarian cancer in individual women. Thus, epidemiologists will need to collaborate with scientists in other fields (eg, biostatisticians, data scientists, clinicians) to integrate data on genetics, other omics, and nongenetic risk factors to improve individual-level risk prediction models and identification of women who will benefit most from screening and risk-reducing surgeries.

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Exhibit 126

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ORIGINAL PAPER

Benign gynecologic conditions are associated with ovarian cancer risk in African-American women: a case–control study

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Abstract

Background The association between common benign gynecologic conditions and ovarian cancer remains under-studied in African Americans. Therefore, we examine the association between self-reported history of benign gynecologic conditions and epithelial ovarian cancer risk in African-American women.

Methods Data from a large population-based, multi-center case–control study of epithelial ovarian cancer in African-American women were analyzed to estimate the association between self-reported history of endometriosis, pelvic inflammatory disease (PID), fibroid, and ovarian cyst with epithelial ovarian cancer. Logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI) for the associations between individual and composite gynecologic conditions and ovarian cancer.

Results 600 cases and 752 controls enrolled in the African American Cancer Epidemiology Study between 1 December 2010 and 31 December 2015 comprised the study population. After adjusting for potential confounders, a history of endometriosis was associated with ovarian cancer (OR 1.78; 95% CI 1.09–2.90). A non-significant association of similar magnitude was observed with PID (OR 1.33; 95% CI 0.82–2.16), while no association was observed in women with a history of fibroid or ovarian cyst. A positive trend was observed for an increasing number of reported gynecologic conditions ($p=0.006$) with consistency across histologic subtypes and among both oral contraceptive users and non-users.

Conclusion A self-reported history of endometriosis among African-American women was associated with increased risk of ovarian cancer. Having multiple benign gynecologic conditions also increased ovarian cancer risk.

Keywords Ovarian cancer · African-American · Endometriosis · Pelvic inflammatory disease (PID) · Ovarian cyst · Uterine fibroid · African-American Cancer Epidemiology Study (AACES)

Abbreviations

PID	Pelvic inflammatory disease
OC	Oral contraceptive
AACES	African-American Cancer Epidemiology Study
SEER	Surveillance, Epidemiology, and End Results
AJCC	American Joint Committee on Cancer
OR	Odds ratio
CI	Confidence interval
BMI	Body mass index

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Introduction

Accumulating epidemiologic evidence suggests that endometriosis is associated with approximately twofold increased risk of developing non-serous epithelial ovarian cancer [1–4]. Studying the pathophysiology and biologic risk factors associated with endometriosis has helped elucidate potential mechanisms of tumorigenesis in non-serous ovarian cancer subtypes distinct from that of serous carcinoma. Chronic inflammation, aberrant immune response, genetic alterations, and hormonal imbalance marked by excess estrogen have been implicated in the multi-step malignant transformation of benign endometriotic cells [5–8]. The epidemiologic linkage between endometriosis and ovarian cancer and the strength of the associations estimated from studies

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of predominantly white women remain to be confirmed in other race and ethnicities.

Other gynecologic conditions, such as pelvic inflammatory disease (PID) [9–11] and ovarian cyst [12], have been associated with increased risk of ovarian cancer in a small number of studies; however, findings are conflicting [4, 13–16]. The association between uterine fibroids, a condition which disproportionately affects African-American women [17, 18], and ovarian cancer is largely unknown. Any potential association observed between fibroids and ovarian cancer may be modified or confounded by increased rates of hysterectomy and procedure-related interruption of tubal patency and ovarian blood supply in women with fibroids [19–21]. Similarly, oral contraceptive (OC) is frequently prescribed as treatment for benign gynecologic conditions, and OC use could potentially alter the ovarian cancer risk associated with benign gynecologic conditions.

The link between these common benign gynecologic conditions and ovarian cancer remains under-studied in African-Americans. In this study, we explore the relationship between self-reported history of benign gynecologic conditions (endometriosis, PID, uterine fibroid, and ovarian cyst) and epithelial ovarian cancer in African-American women. While the exact biological etiologies remain to be fully elucidated, these gynecologic pathologies all affect a pro-inflammatory milieu. The association between having multiple gynecologic conditions and ovarian cancer was also examined to assess the potential effect of the increased burden of inflammation-related exposures.

Materials and methods

The data used in these analyses were collected as part of the African-American Cancer Epidemiology Study (AACES), a population-based, case–control study of ovarian cancer in African-American women from 11 geographic regions (Alabama, Georgia, Illinois, Louisiana, Michigan, New Jersey, North Carolina, Ohio, South Carolina, Tennessee, and Texas). Study participants completed informed consent prior to enrollment in the study and institutional review board approval was obtained from all participating institutions. The methods of the study have been previously reported in detail [22], and a brief summary of the study methods follows.

Cases were identified through rapid case ascertainment systems using either state cancer registries, Surveillance, Epidemiology, and End Results (SEER) registries, or individual hospital registries. Inclusion criteria were as follows: self-identified African-American/Black race, age 20–79 years at diagnosis, pathology-confirmed invasive epithelial ovarian cancer diagnosis between 1 December 2010 and 31 December 2015, and ability to complete an interview in English. Controls were identified through random digit dialing and frequency matched to cases on 5-year age groups and geographic region. Controls were eligible if they had at least one intact ovary, self-identified as African-American/black race, and were 20–79 years at baseline interview. Accrual began in December 2010, and the current analyses include 600 cases and 752 controls enrolled in the study as of December 2017.

Participants were asked to complete a baseline interviewer-administered, computer-assisted telephone survey. Information collected included demographic characteristics; reproductive, gynecologic and medical history; hormone use; family history of cancer; and lifestyle characteristics such as smoking, alcohol consumption, and physical activity. In addition, participants were asked if they had ever been diagnosed with endometriosis, PID, uterine fibroid or ovarian cyst (yes/no). The interviewer provided a scripted description of the conditions if the participant was not familiar with the medical terminology. If a participant reported a history of these conditions, she was asked to provide the age at first diagnosis. In our analyses, participants who were diagnosed with any gynecologic condition 1 year or less before ovarian cancer diagnosis (cases) or interview date (controls) were coded as not having the condition to reduce surveillance bias. A sensitivity analysis (diagnosis of gynecologic condition 3, 5, or 10 years or less before ovarian cancer diagnosis or baseline interview coded as not having the condition) was performed to evaluate the length of time between diagnosis of gynecologic condition and the referent date (ovarian cancer diagnosis or baseline interview) and its association with ovarian cancer risk.

Overall, 8.7% of cases and 2.5% of controls completed a shorter version of the survey. All variables examined in our analysis were ascertained in both the long and short versions of the survey. Missing data for endometriosis (4 cases), fibroid (1 cases), PID (5 cases, 2 controls), and ovarian cyst (1 control) were conservatively coded as not having the condition. The distribution of demographic and descriptive characteristics, including frequency of reported gynecologic conditions, between cases and controls was compared using Student's t-test and Chi-square test for continuous and categorical/ordinal variables, respectively. For cases, the mean age at ovarian cancer diagnosis was compared among those with and without a history of each gynecologic condition using Student's *t* test. In addition, the distribution of histologic subtype and American Joint Committee on Cancer (AJCC) stage was summarized by gynecologic condition.

Logistic regression analyses were performed to calculate odds ratios (OR) and 95% confidence intervals (CI) for the associations between history of endometriosis, PID, uterine fibroid or ovarian cyst and the risk of ovarian cancer. Known or potential confounders were selected a priori and included in the multivariable model as follows: reference age (age at

diagnosis for cases, age at baseline interview for controls) category (20–29, 30–49, 50–69, 70–79), geographic region (South/mid-Atlantic, South Central, Midwest), marital status (single/never married, married/living with partner, divorced/separated/widowed), education (high school or less, some post-high school training, college or graduate degree), body mass index (BMI in kg/m^2, continuous variable), parity (0, 1, 2, 3 or more), tubal ligation (yes/no), duration of OC use (never, <60 months, ≥ 60 months), first degree family history of breast or ovarian cancer (yes/no), talc use (never use, any genital use, non-genital use only), endometriosis (yes/no), PID (yes/no), fibroid (yes/no), and ovarian cyst (yes/no). An expanded regression model additionally included hysterectomy status (yes/no) to examine the potential confounding effect of hysterectomy. Hysterectomy status was limited to those performed more than 1 year before the ovarian cancer diagnosis or baseline interview to reduce detection bias.

To explore a potential dose–response relationship, multivariable logistic regression analyses were performed to calculate the association between the total number of benign conditions (0, 1, 2, or more) and risk of ovarian cancer. ORs are reported from categorical models and *p* values for trend are reported from continuous models to test for the linear trend related to an increasing number of benign conditions. The referent group was women with no history endometriosis, PID, fibroid, or ovarian cyst.

The association between the benign conditions and ovarian cancer risk was further examined in a stratified analysis by histologic subtype (serous/non-serous). Non-serous subtypes were further stratified into endometrioid, mucinous, clear cell, or other subtype in a supplemental analysis. In addition, the potential modifying effect of OC use on ovarian cancer risk associated with gynecologic conditions was evaluated in a stratified analysis by history of OC use (never use/ever use). The interaction between history of OC use and gynecologic conditions was assessed by including a multiplicative term in the models. All statistical analyses were performed using SAS version 9.3 (Cary, North Carolina).

Results

600 cases and 752 controls were included in the analysis. Comparison of demographic and clinical characteristics of cases and controls is presented in Table 1. Cases were older, less likely to be married or living with a partner, and less likely to have post-high school education compared to controls. Cases also were more likely to report having a first degree female relative with breast or ovarian cancer, former smoking, genital talc use, and nulliparity, compared to controls. Cases were less likely to report history of tubal ligation or OC use, but the proportion reporting hysterectomy was similar between the two groups. Cases were more likely to report endometriosis (8.2% vs. 4.4%, $p=0.004$) and PID (7.3% vs. 4.7%, $p=0.037$). There was no difference in the reporting of uterine fibroid (41.7% vs. 36.6%, $p=0.056$) and ovarian cyst between cases and controls (13.3% vs. 11.2%, $p=0.226$).

The association between benign gynecologic conditions and risk of epithelial ovarian cancer is shown in Table 2. A history of endometriosis was associated with ovarian cancer (OR 1.78; 95% CI 1.09–2.90) after adjusting for age, study site, marital status, education, BMI, parity, tubal ligation, duration of OC use, family history of breast or ovarian cancer, talc use, and history of PID, fibroid or ovarian cyst. The adjustment variables are all suggested risk factors for ovarian cancer and some are more common in the African American community. For example, talc use is highly prevalent in the African American community and excluding this variable over-estimated the associations in our analysis (data not shown).

An association was observed in women with a history of PID (OR 1.33; 95% CI 0.82–2.16), although the result did not reach statistical significance. While no association was observed in women with a history fibroid (OR 1.10; 95% CI 0.86–1.40) and ovarian cyst (OR 1.18; 95% CI 0.92–1.52), a positive trend of increasing OR was observed with increasing number of benign gynecologic conditions ($p=0.006$). For women who reported 2 or more gynecological conditions, 31% had PID, 37% had endometriosis, 64% had cysts, and 93% had fibroids. Direction and magnitude of associations remained essentially unchanged when hysterectomy status was included in the regression model or when the gynecologic diagnosis was censored at 3, 5, and 10 years from the referent date (data not shown).

The relationship between benign gynecologic conditions and epithelial ovarian cancer stratified by serous vs. non-serous histology is shown in Table 3. Endometriosis was associated with a near threefold increase in non-serous ovarian cancer (OR 2.80; 95% CI 1.53–5.10). Odds of serous ovarian cancer was also increased among women with a history of endometriosis, but the association was not significant (OR 1.29; 95% CI 0.71–2.35). Similarly, non-significant associations were observed for PID with both serous (OR 1.65; 95% CI 0.98–2.79) and non-serous (OR 0.90; 95% CI 0.42–1.91) ovarian cancer. No histologic subtype-specific association was observed with history of fibroid, or ovarian cyst. The risk of both serous and non-serous ovarian cancer increased with increasing number of benign gynecologic conditions. A history of 2 or more conditions was associated with a 1.5- to 2-fold increased risk of serous (OR 1.51; 95% CI 1.00–2.29) and non-serous ovarian cancer (OR 2.13; 95% CI 1.32–3.46). Further analysis of non-serous ovarian cancer stratified by histologic subtypes suggested positive associations between endometriosis

Table 1 Demographic and clinical characteristics of ovarian cancer cases and controls in the African American Cancer Epidemiology Study

Characteristics	Total $n=1,352$ (%)	Cases $n=600$ (%)	Control $n=752$ (%)	p value
Age (mean years, range)	56.3 (20–79)	58.1 (20–79)	55.0 (20–79)	<0.001
BMI (kg/m^2)	32.3 (14.8–78.3)	32.8 (14.8–74.4)	32.0 (15.9–78.3)	0.064
Marital status				0.001
Single, never married	328 (24.3)	144 (24.0)	184 (24.5)	
Married or living with partner	509 (37.6)	197 (32.8)	312 (41.5)	
Divorced/separated or widowed	515 (38.1)	259 (43.2)	256 (34.0)	
Education				0.021
High school or less	550 (40.7)	269 (44.8)	281 (37.4)	
Some post-high school training	358 (26.5)	147 (24.5)	211 (28.1)	
College or graduate degree	444 (32.8)	184 (30.7)	260 (34.6)	
Menstrual status				0.171
Pre/peri-menopause	386 (28.6)	160 (26.7)	226 (30.1)	
Menopause	966 (71.4)	440 (73.3)	526 (69.9)	
Medical history				
Pulmonary disease[a]	220 (16.3)	96 (16.0)	124 (16.5)	0.809
Diabetes	315 (2,336)	137 (22.8)	178 (23.7)	0.718
Cardiac disease[b]	147 (10.9)	64 (10.7)	83 (11.0)	0.828
Hypertension	829 (61.3)	403 (67.2)	426 (56.7)	<0.001
Anemia	451 (33.3)	236 (39.3)	215 (28.6)	<0.001
1st degree female relative with breast/ovarian cancer				<0.001
Yes	292 (21.6)	158 (26.3)	134 (17.8)	
No	1,060 (78.4)	442 (73.7)	618 (82.2)	
Cigarette smoking				<0.001
Never smoker	769 (56.9)	332 (55.3)	437 (58.1)	
Current smoker	209 (15.5)	61 (10.2)	148 (19.7)	
Former smoker	374 (27.7)	207 (34.5)	167 (22.2)	
Talc use				<0.001
Never use	578 (42.8)	224 (37.3)	354 (47.1)	
Any genital use	519 (38.4)	264 (44.0)	255 (33.9)	
Non-genital use only	255 (18.9)	112 (18.7)	143 (19.0)	
Parity (# of live births)				0.033
0	207 (15.3)	111 (18.5)	96 (12.8)	
1	251 (18.6)	108 (18.0)	143 (19.0)	
2	345 (25.5)	144 (24.0)	201 (26.7)	
3+	548 (40.6)	236 (39.4)	312 (41.5)	
Tubal ligation				0.060
Yes	513 (37.9)	211 (35.2)	302 (40.2)	
No	839 (62.1)	389 (64.8)	450 (59.8)	
OC use				<0.001
Never	346 (25.6)	188 (31.3)	158 (21.0)	
<60 months	574 (42.5)	237 (39.5)	337 (44.8)	
≥60 months	432 (32.0)	175 (29.2)	257 (34.2)	
Hysterectomy[c]				0.605
Yes	311 (23.0)	142 (23.7)	169 (22.5)	
No	1,041 (77.0)	458 (76.3)	583 (77.5)	
Benign gynecologic condition[d]				
Endometriosis	82 (6.1)	49 (8.2)	33 (4.4)	0.004
PID	79 (5.8)	44 (7.3)	35 (4.7)	0.037
Fibroid	525 (38.8)	250 (41.7)	275 (36.6)	0.056
Ovarian cyst	164 (12.1)	80 (13.3)	84 (11.2)	0.226

Table 1 (continued)

Characteristics	Total $n=1,352$ (%)	Cases $n=600$ (%)	Control $n=752$ (%)	p value
Histology				
High-grade serous		365 (60.8)		
Low-grade serous		17 (2.8)		
Endometrioid		56 (9.3)		
Clear cell		20 (3.3)		
Mucinous		31 (5.2)		
Carcinosarcoma		16 (2.7)		
Other[e]		75 (12.5)		
Missing		20 (3.3)		
Stage				
I/II		188 (31.3)		
III/IV		366 (61.0)		
Unknown		46 (7.7)		

Missing or unknown data: BMI (4 cases, 1 control), parity (1 case)

BMI body mass index, *OC* oral contraceptive, *PID* pelvic inflammatory disease

[a]Include asthma, emphysema, bronchitis

[b]Include angina, congestive heart failure, coronary artery disease

[c]Surgery completed > 1 year before ovarian cancer diagnosis or interview for indications other than ovarian cancer

[d]Diagnosis made > 1 year before ovarian cancer diagnosis or interview

[e]Include mixed, NOS, other invasive epithelial ovarian carcinoma, borderline serous

Table 2 Crude and adjusted odds ratios for the association between epithelial ovarian cancer and benign gynecologic conditions by type and number of condition

Gynecologic conditions	Cases (%)	Control (%)	Crude OR	95% CI	Adjusted OR[a]	95% CI
Type of gynecologic conditions						
Endometriosis						
No	551 (91.8)	719 (95.6)	1.00	Referent	1.00	Referent
Yes	49 (8.2)	33 (4.4)	1.94	1.23–3.05	1.78	1.09–2.90
PID						
No	556 (92.7)	717 (95.4)	1.00	Referent	1.00	Referent
Yes	44 (7.3)	35 (4.7)	1.62	1.03–2.56	1.33	0.82–2.16
Fibroid						
No	350 (58.3)	477 (63.4)	1.00	Referent	1.00	Referent
Yes	250 (41.7)	275 (36.6)	1.24	0.99–1.54	1.10	0.86–1.40
Ovarian cyst						
No	520 (86.7)	668 (88.8)	1.00	Referent	1.00	Referent
Yes	80 (13.3)	84 (11.2)	1.22	0.88–1.70	1.18	0.83–1.69
# of gynecologic conditions						
0	294 (49.0)	420 (55.9)	1.00	Referent	1.00	Referent
1	214 (35.7)	255 (33.9)	1.20	0.95–1.52	1.18	0.92–1.52
2+	92 (15.3)	77 (10.2)	1.71	1.22–2.39	1.66	1.16–2.38
			p trend = 0.002		p trend = 0.006	

Diagnosis made > 1 year before ovarian cancer diagnosis or interview

OR odds ratio, *CI* confidence interval, *PID* pelvic inflammatory disease, # number

[a]Fully adjusted model—adjusted for age at diagnosis (cases)/interview (control), study site, marital status, education, BMI, parity, tubal ligation, duration of oral contraceptive use, family history of breast or ovarian cancer, talc use, endometriosis, fibroid, PID, ovarian cyst. OR for # of gynecologic conditions not adjusted for endometriosis, fibroid, PID, ovarian cyst

Table 3 Crude and adjusted odds ratios for the association between epithelial ovarian cancer and benign gynecologic conditions stratified by histologic subtypes (serous vs. non-serous)

Benign gynecologic condition	Histologic subtype	Cases (%)	Adjusted OR[a]	95% CI
Endometriosis				
No	Serous	362 (94.3)	1.00	Referent
Yes		22 (5.7)	1.29	0.71–2.35
No	Non-serous	169 (86.2)	1.00	Referent
Yes		27 (13.8)	2.80	1.53–5.10
PID				
No	Serous	351 (91.4)	1.00	Referent
Yes		33 (8.6)	1.65	0.98–2.79
No	Non-serous	185 (94.4)	1.00	Referent
Yes		11 (5.6)	0.90	0.42–1.91
Fibroid				
No	Serous	228 (59.4)	1.00	Referent
Yes		156 (40.6)	1.08	0.82–1.43
No	Non-serous	109 (55.6)	1.00	Referent
Yes		87 (44.4)	1.22	0.85–1.75
Ovarian cyst				
No	Serous	335 (87.2)	1.00	Referent
Yes		49 (12.8)	1.16	0.76–1.75
No	Non-serous	167 (85.2)	1.00	Referent
Yes		29 (14.8)	1.13	0.68–1.90
# of gynecologic conditions				
0	Serous	192 (50.0)	1.00	Referent
1		138 (35.9)	1.18	0.89–1.57
2+		54 (14.1)	1.51	1.00-2.29
			p trend = 0.044	
0	Non-serous	91 (46.4)	1.00	Referent
1		67 (34.2)	1.20	0.82–1.75
2+		38 (19.4)	2.13	1.32–3.46
			p trend = 0.004	

Diagnosis made > 1 year before ovarian cancer diagnosis or interview

OR odds ratio, *CI* confidence interval, *PID* pelvic inflammatory disease

[a]Fully adjusted model—adjusted for age at diagnosis (cases)/interview (control), study site, marital status, education, BMI, parity, tubal ligation, duration of oral contraceptive use, family history of breast or ovarian cancer, talc use, endometriosis, fibroid, PID, ovarian cyst. OR for # of gynecologic conditions not adjusted for endometriosis, fibroid, PID, ovarian cyst

and endometrioid (OR 5.17; 95% CI 2.30–11.64) and ovarian cysts with mucinous subtype (OR 3.35; 95% CI 1.33–8.44) (Table S1).

In analyses stratified by history of OC use, there was no consistent pattern or evidence of strong effect modification by OC use on the association between benign gynecologic conditions and ovarian cancer risk (Table 4). The association between endometriosis and ovarian cancer was more pronounced among OC ever- vs. never-users (OR 1.92; 95% CI 1.13–3.24 vs. OR 1.44; 95% CI 0.34–6.31). However, for PID, fibroid, ovarian cyst, and a history of 2 or more benign conditions, the trend was reversed. Test of interaction was not significant for any gynecologic condition.

Discussion

In this analysis of a large, population-based case–control study of African-American women, a history of at least one benign gynecologic condition was reported by approximately half of cases and controls. We observed a consistent association between a history of endometriosis and epithelial ovarian cancer. A consistently positive but non-significant association was observed with PID, while no apparent association was observed with fibroid or ovarian cyst. Having multiple conditions consistently showed a trend towards increased risk of ovarian cancer across histologic subtypes.

Table 4 Crude and adjusted odds ratios for the association between epithelial ovarian cancer and benign gynecologic conditions stratified by oral contraceptive use

Benign gynecologic condition	Oral contraceptive use	Cases (%)	Control (%)	Adjusted OR[a]	95% CI	$p_{interaction}$
Endometriosis						0.450
No	OC never use	180 (95.7)	155 (98.1)	1.00	Referent	
Yes		8 (4.3)	3 (1.9)	1.45	0.34–6.31	
No	OC ever use	371 (90.0)	564 (95.0)	1.00	Referent	
Yes		41 (10.0)	30 (5.1)	1.92	1.13–3.24	
PID						0.197
No	OC never use	176 (93.6)	153 (96.8)	1.00	Referent	
Yes		12 (6.4)	5 (3.2)	1.87	0.59–5.95	
No	OC ever use	380 (92.2)	564 (95.0)	1.00	Referent	
Yes		32 (7.8)	30 (5.1)	1.31	0.76–2.26	
Fibroid						0.703
No	OC never use	118 (62.8)	116 (73.4)	1.00	Referent	
Yes		70 (37.2)	42 (26.6)	1.23	0.73–2.06	
No	OC ever use	232 (56.3)	361 (60.8)	1.00	Referent	
Yes		180 (43.7)	233 (39.2)	1.06	0.80–1.40	
Ovarian cyst						0.127
No	OC never use	160 (85.1)	146 (92.4)	1.00	Referent	
Yes		28 (14.9)	12 (7.6)	1.88	0.84–4.20	
No	OC ever use	360 (87.4)	522 (87.9)	1.00	Referent	
Yes		52 (12.6)	72 (12.1)	1.00	0.66–1.51	
# of gynecologic conditions						0.483
0	OC never use	104 (55.3)	108 (68.4)	1.00	Referent	
1		57 (30.3)	39 (24.7)	1.38	0.81–2.33	
2+		27 (14.4)	11 (7.0)	2.36	1.07–5.19	
				p trend = 0.024		
0	OC ever use	190 (46.1)	312 (52.5)	1.00	Referent	
1		157 (38.1)	216 (36.4)	1.12	0.84–1.50	
2+		65 (15.8)	66 (11.1)	1.53	1.01–2.30	
				p trend = 0.055		

Diagnosis made > 1 year before ovarian cancer diagnosis or interview

OR odds ratio, *CI* confidence interval, *dz*. disease, *PID* pelvic inflammatory disease

[a]Fully adjusted model—adjusted for age at diagnosis (cases)/interview (control), study site, marital status, education, BMI, parity, tubal ligation, family history of breast or ovarian cancer, talc use, endometriosis, fibroid, PID, ovarian cyst. OR for # of gynecologic conditions not adjusted for endometriosis, fibroid, PID, ovarian cyst

The most consistent association in our study was observed in women with a history of endometriosis, with increased risk seen across multiple analyses despite the relatively small number of women with the condition. Positive associations between endometriosis and clear cell and endometrioid subtypes confirm findings previously reported in population-based studies of primarily white women [1–4]. The risk of ovarian cancer in women with endometriosis may vary depending on diagnostic criteria used (clinical only vs. surgical-pathological confirmation), but approximate two-fold increased risk observed in our study is consistent with findings from the majority of studies examining women with self-reported history of endometriosis (OR 1.3–1.9) [1, 4, 23–26]. Women with a history of endometriosis also had higher odds of being diagnosed with serous ovarian cancer, but the association was not significant. Association between endometriosis and serous ovarian cancer has not been established in existing studies. A recent pooled analysis by Pearce et al. was the first to separately examine the association with high- vs. low-grade serous ovarian cancer and to report a positive association with only low-grade serous subtype [1]. Small sample size in our study precluded further stratification by tumor grade.

Despite the well-established epidemiologic linkage, underlying biological mechanisms driving the association between endometriosis and non-serous ovarian cancer remain to be fully elucidated. Histologically, increased rates of severe atypia with or without complex hyperplasia has

been observed in endometriotic implants adjacent to ovarian carcinoma [2, 6]. This suggests a possible multi-step transformation from benign endometriotic cells to carcinoma aided by the pro-inflammatory microenvironment, altered immune response, and hormonal imbalance. Molecular and genetic studies examining the association between endometriosis and ovarian cancer support the association [7].

We consistently observed an approximate 1.5-fold (up to 1.8-fold among OC never users) increase in ovarian cancer risk among women with a history of PID suggesting a modest association. Observed associations were not consistently significant, but this may be attributed to limitations in sample size and smaller effect size. A small number of case–control and cohort studies have found a 1.5- to twofold increased risk of ovarian cancer in women with a history of PID [9–11], but other studies have reported conflicting results [4, 13, 14]. A recent large pooled analysis of 13 population-based case–control studies found no association between PID and overall ovarian cancer risk, but reported increased risks of low-grade serous and endometrioid subtypes [23]. In our histologic subtype analyses, we observed a positive association with clear cell subtype, but not with endometrioid subtype. Possible linkage with low-grade serous, endometrioid and clear cell subtypes may suggest a shared pro-inflammatory pathway with endometriosis. Supplemental histologic subtype analysis was limited in sample size and exploratory in nature. These results must be interpreted with caution and await further confirmation.

We did not find associations between overall ovarian cancer and a history of fibroid or ovarian cyst, but increasing number of gynecologic conditions was consistently associated with increased risk of ovarian cancer, including both serous and non-serous subtypes. The risk associated with serous ovarian cancer in women with a history of multiple conditions was higher than individual associations observed in any one gynecologic condition. This observation may suggest a possible additive or synergistic effect on tumorigenesis influenced by the pro-inflammatory milieu from an increased burden in the number of benign conditions. Increased risk of serous ovarian cancer in women with other pro-inflammatory risk factors has been reported, most notably in talc users [4, 24].

Direction and magnitude of association and underlying biological mechanism contributing to ovarian cancer tumorigenesis are likely to vary by type of ovarian cyst pathology. Ovarian cyst can represent a wide range of pathologies from functional cysts to benign tumors to endometriomas, which are a type of endometriosis. Existing results vary widely from minimal to no ovarian cancer risk associated with symptomatic functional or stable simple ovarian cyst to twofold or greater increased risk if concomitant infertility or endometrioma is present [15, 16, 25, 26]. An association between ovarian cyst and mucinous ovarian cancer was observed in our histologic subtype analysis. The association between a history of ovarian cyst and mucinous ovarian cancer has not been previously reported, but the linkage is biologically plausible. Positive associations between self-reported history of ovarian cyst and mucinous borderline tumor, believed to be a precursor of invasive mucinous carcinoma, have been reported [12, 16]. More studies are needed to identify the epidemiologic risk factors for mucinous carcinoma, which appear to have molecular and genetic underpinnings distinct from other non-serous subtypes.

Overall, a history of OC use was common among both cases and controls, especially among women with gynecologic conditions. The well-established protective effect of OC has been hypothesized to be mediated by ovulation suppression, reduction in gonadotropins, and increase in apoptosis induced by increased progestin level [27, 28]. In the presence of gynecologic disease, OC may further help modulate ovarian cancer development by preventing hormonal stimulation of endometriotic cells, fibroid, and ovarian cyst and reducing the risk of recurrent PID. We explored the effect of OC use on gynecologic condition-related ovarian cancer risk in a stratified analysis. Overall, OC use did not appear to have a strong or consistent influence on the pattern of associations between benign gynecologic conditions and ovarian cancer beyond the known general protective effect.

This study has limitations that should be considered when interpreting the findings. The prevalence of the gynecologic conditions was based on unverified self-report and subject to misclassification and recall bias. The misclassification may be compounded by the relatively subjective nature of endometriosis or PID diagnosis. Additionally, endometrioma represents a type of ovarian cyst arising from endometriosis and may be reported as a history of ovarian cyst alone. As we do not have information on the type of ovarian cyst in our study, we are not able to estimate the prevalence of this misclassification. To reduce the potential surveillance bias, gynecologic conditions diagnosed within 1 year before ovarian cancer diagnosis or interview date were recoded as not having the condition. We cannot exclude the possibility of bias related to increased intensity and duration of surveillance for more severe disease; however, cases were less likely to have had a health check-up within 2 years and a sensitivity analysis censoring gynecologic diagnosis to 3, 5, or 10 years before ovarian cancer diagnosis demonstrated consistent associations. We also acknowledge that bias due to confounding by treatment of gynecologic conditions other than OC may exist. In our study, hysterectomy was not associated with ovarian cancer, nor did it appear to modify the association between benign gynecologic condition and ovarian cancer. The rate of unilateral oophorectomy among women with ovarian cysts was higher among controls (14 of 84) compared to cases (6 of 85), but small numbers did not allow subgroup analysis.

Our results represent findings from the largest case–control study of African-American women with ovarian cancer in the U.S. to date. Moreover, unlike reports from secondary analysis of other studies, AACES was specifically designed to investigate risk factors associated with ovarian cancer in African-American women. The large number of participants in our study allowed examination of associations between several common gynecologic conditions and ovarian cancer while adjusting for multiple confounders and known risk factors. In particular, talc powder use is highly prevalent in the African-American community and has been found to be associated with increased risk of ovarian cancer in this and other studies [4, 24, 29]. Indeed, regression models excluding talc use over-estimated the associations in our analyses.

In summary, we report positive associations between a self-reported history of endometriosis, and to a lesser degree PID, with ovarian cancer risk in African-American women similar to existing reports among non-African-American populations. Having more than one benign gynecologic condition also increased ovarian cancer risk.

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Author contributions JS, HP, and MC contributed to the conception and design of the study, analysis and interpretation of data, and drafting of the manuscript. JS, AA, JBS, EF, PT, JJR, and AS contributed to the interpretation of the data and critical revision of the manuscript. All authors reviewed and gave approval of the final version to be published.

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Compliance with ethical standards

Ethics approval and consent to participate The study protocol and questionnaire were approved by the Institutional Review Boards at Duke University Medical Center, Baylor College of Medicine, Case Western Reserve University School of Medicine, Louisiana State University, Robert Wood Johnson Medical School/Rutgers Cancer Institute, Wayne State University, the University of Alabama-Birmingham, the Medical University of South Carolina, and the University of Tennessee-Knoxville. Additionally, the protocol was approved by central cancer registries in the states of Alabama, Georgia, North Carolina, South Carolina, Tennessee, and Texas, SEER registries in New Jersey, Louisiana, and the Detroit metropolitan area, and 9 individual hospital systems in Ohio. All study participants completed informed consent prior to enrollment.

Availability of data and materials The dataset used and analyzed in this study is available after review from the AACES study investigators and with proper IRB approvals.

Conflict of interest The authors declare that they have no competing interests.

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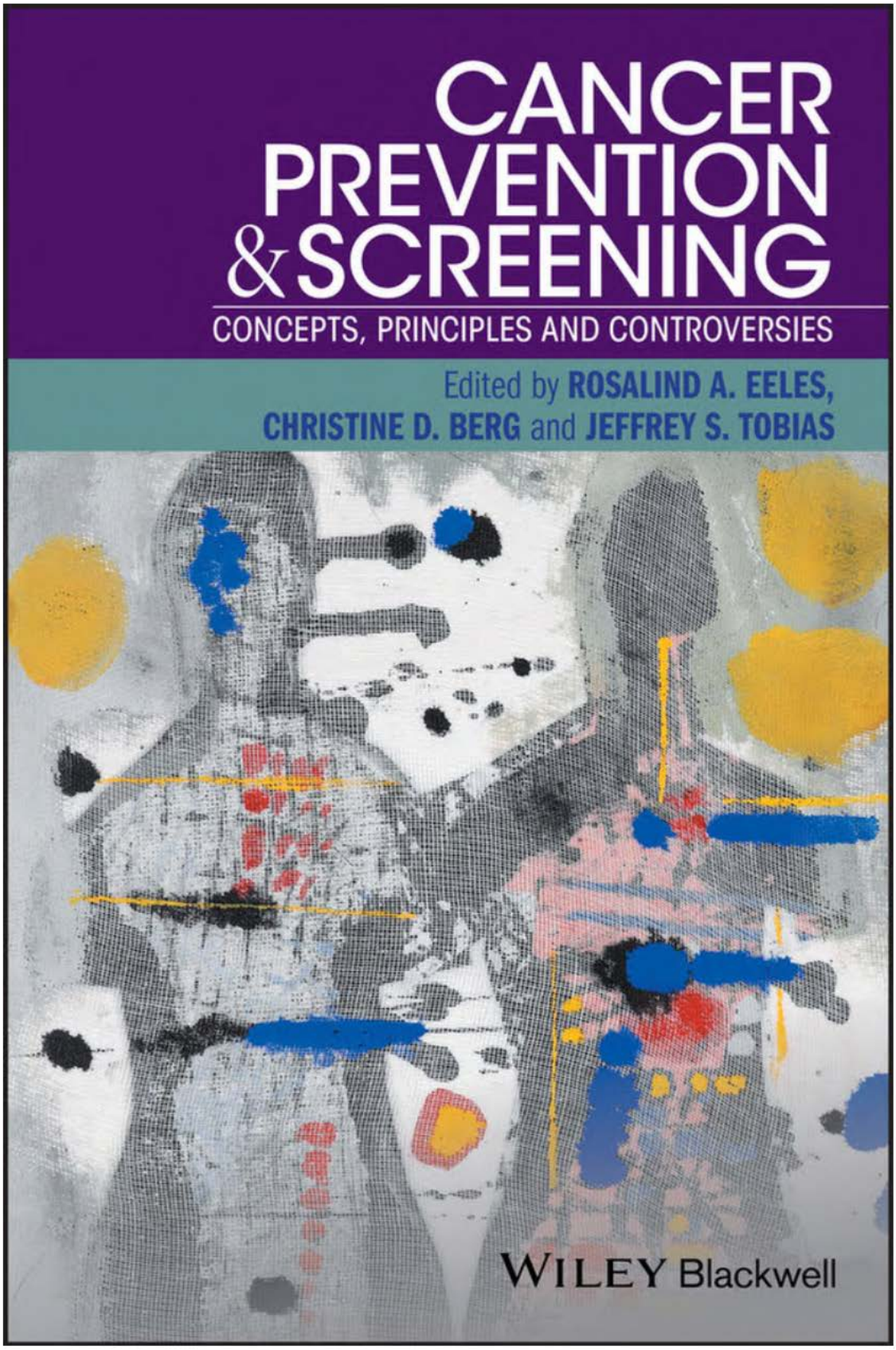
Exhibit 127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Cancer prevention and screening

Concepts, principles and controversies

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CHAPTER 23

Ovarian cancer prevention and screening

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SUMMARY BOX

- Major efforts have been made to identify risk factors for ovarian cancer and to build risk-prediction models that combine epidemiological, genetic, and epigenetic factors in order to improve risk stratification.
- Future preventive strategies such as the oral contraceptive pill, aspirin, and opportunistic salpingectomy and screening strategies are likely to be based on individual risk estimates using such models.
- There is good evidence that multimodal screening using serum CA125 interpreted using ROCA with TVS as a second-line test has encouraging performance characteristics.
- Screening for ovarian cancer in the general population is currently not recommended. However, results of the UK Collaborative Trial of Ovarian Cancer Screening suggest a mortality reduction associated with multimodal screening of around 20%. If this is confirmed on further follow-up of two to three years, it is likely to have an impact on future recommendations.
- Women at high risk are advised to undergo risk-reducing salpingo-oophorectomy. For those opting not to undergo surgery, in the UK screening is currently not available on the NHS, but is advocated at six-monthly intervals in the USA.
- A drive to develop a new generation of screening tests based on tumour DNA and novel specimens such as cervical samples is under way.

Ovarian cancer (OC) is the most fatal of all gynaecological malignancies and accounts for around 4% of all cancers diagnosed in women. Worldwide, there are 239 000 new cases of OC each year, of whom 7270 are in the UK [1]. While 10-year age-standardized survival has increased in England from 18% during 1971–1972 to 35% during 2010–2011, two-thirds of women die within 10 years of diagnosis [2]. Most of the improvement in survival has occurred in early-stage

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disease, highlighting the importance of diagnosing early-stage/low-volume disease. This has led to ongoing efforts to explore risk stratification, prevention, and screening, which form the focus of this chapter. Given that epithelial OC is a heterogeneous disease, it is unlikely that one strategy will be effective for all histological subtypes (high-grade serous, endometrioid, clear-cell, low-grade serous, mucinous). In addition, recent evidence on precursor lesions such as serous tubal intraepithelial carcinoma (STIC) in a proportion of high-grade serous cancers suggests the need to explore novel solutions beyond routine tests such as serum CA125 and transvaginal ultrasound.

Lifetime risk of ovarian cancer

The average woman's lifetime risk of ovarian cancer is 1.9% [3], but there are women at substantially higher (40–60%) and lower risk. It is increasingly possible to stratify women based on their genetic and epidemiological risk factors [3].

Risk factors

Age

There is a strong correlation with age, with 83% of cases occurring in women over 50 years. The incidence rates rise sharply from an age-standardized rate of 8.9 per 100 000 in women aged 35–39 to a peak of 69.2 per 100 000 in those aged 80–84 [4].

Family history

The strongest risk factor is a family history of breast and multiple ovarian cancers [5] or the Lynch syndrome cancers (bowel, endometrium, stomach, kidney, ovary, skin in multiple relatives) [6, 7]. Women with a single first-degree relative with ovarian cancer may have up to a threefold increased risk [8]. Genetic predisposition could be due to alterations in the following:

High-penetrance genes

These include mutations in the *BRCA1* and *BRCA2* genes, with average cumulative risk of epithelial OC by the age of 70 of 40–60% (*BRCA1*) and 11–27% (*BRCA2*) mutation carriers [9]. Emerging evidence suggests that *BRCA* germline mutations are present in 14% of women with invasive nonmucinous epithelial ovarian cancer, and 22% of those with high-grade serous epithelial ovarian cancer [10]. This has led to efforts to extend genetic testing for *BRCA* genes to all women with nonmucinous epithelial OC at the point of diagnosis. *BRCA* mutations occur at a rate of 1 in 300 to 1 in 500 in most populations [11], but significantly increase to 1 in 40 in the Ashkenazi Jewish population [11]. In the latter group, there is growing evidence that identification of individuals through family history alone misses over half of those with mutations in *BRCA1/2*

[12–15]. Using systematic testing in such populations with a high prevalence of mutations has recently been shown to be acceptable and cost-effective [16], and suggests that 3.6% of OCs could be prevented if population testing for *BRCA1/2* was available [17].

In Lynch syndrome, the lifetime risk of OC is lower and related to the specific mutations (approximately 2–15%) [18] in at least five different DNA mismatch repair genes [19], with the highest risk in *MLH1* and *MSH2* carriers.

Moderate-penetrance genes

Several susceptibility genes that confer more moderate penetrance risks of OC, such as *RAD51C* [20, 21], *RAD51D* [22], and *BRIP1* [23], have been described and may account for the excess familial risk in these women. The magnitude of risk associated with these alleles seems to be similar to those associated with *BRCA2* mutations. Most recent data suggest that *RAD51C* mutations are associated with a 6.8-fold increased risk of OC, *RAD51D* with a 10-fold increased risk [24], while *BRIP1* deleterious mutations carry a relative risk of OC of 11, increasing to 14 for high-grade serous OCs [25]. Some of these moderate-penetrance genes have been included in commercially available gene-testing panels for ovarian (OvaNEXT™) and breast and ovarian cancer (GeneDX™), without sufficient evidence to support their clinical significance. These multigene panels are constrained by the accuracy of prediction/definition of risk and clinical use [26].

Low-penetrance inherited genetic variants

Through the efforts of the Ovarian Cancer Association Consortium, a worldwide initiative currently consisting of 76 groups, 37 common low-risk (low-penetrance) loci have been identified [27–37], with the strongest association with the serous subtype. Subtype-specific single-nucleotide polymorphisms (SNPs) for the other histological subtypes have also been identified [38]. Individually, these loci confer an increase in relative risk of 1.2–1.4. Despite possible risk stratification based on these SNPs, the clinical implications are still not clear. Some of these loci have been shown to alter OC risk in mutation carriers, with four of these being associated with OC risk in *BRCA2* carriers and two in *BRCA1* carriers [39]. Despite the huge effort in identifying new disease susceptibility loci, the known genetic factors identified so far only account for less than half of the heritable risk for OC [8]. This indicates that other susceptibility alleles exist and that only a fraction of the risk variants have been identified. A major consortia-wide effort (Collaborative Oncological Gene-environment Study, COGS) has contributed to identifying some of the 37 loci included above [29]. However, risk stratification based on the emerging genetic factors will need to be carefully thought through [40].

Epidemiological factors

Established protective factors for OC include oral contraceptive pill (OCP) use, pregnancy, breast-feeding, and tubal ligation, thought to exert their effect through reduction of the number of ovulatory cycles in a woman, while nulliparity and infertility are associated with increased risk (Table 23.1). Of particular interest is

Table 23.1 Risk factors for ovarian cancer (OC).

Risk Factor	OR/RR	95% CI	Author	Year
Oral contraceptive pill (OCP)	0.73	0.66–0.81	Havrilesky et al. [85]	2013
OCP duration (>120 months)	0.43	0.37–0.51		
OCP age at first use (<20)	0.63	0.45–0.89		
OCP type (combined)	0.68	0.55–0.83	Faber et al. [86]	2013
OCP type (combined and progestin only)	0.5	0.28–0.87		
OCP type (progestin only)	0.97	0.45–2.14		
Tubal ligation	0.82	0.68–0.97	Rice et al. [41]	2013
Tubal ligation* (adjusted for age, OCP use, parity)	0.33	0.16–0.64	Hankinson et al. [87]	1993
Tubal ligation	0.87	0.78–0.98	Madsen et al. [44]	2015
Primary invasive epithelial ovarian cancer				
Serous	0.92	0.79–1.08		
Endometrioid	0.66	0.47–0.93		
Mucinous	1.25	0.94–1.67		
Clear cell	1.03	0.65–1.62		
Other	0.6	0.43–0.83		
Borderline	1.03	0.89–1.21		
Salpingectomy			Madsen et al. [44]	2015
Unilateral	0.9	0.72–1.12		
Bilateral	0.58	0.36–0.95		
Hysterectomy with unilateral oophorectomy	0.65	0.45–0.94	Rice et al. [41]	2013
Simple hysterectomy	1.09	0.83–1.42		
Age ≥45	0.64	0.40-1.02		
Underwent procedure within 10 years of questionnaire	0.65	0.38–1.13		
Overall (regardless of year of OC diagnosis)	0.81	0.72–0.92	Jordan et al. [43]	2013
Median year of OC diagnosis pre-2000	0.7	0.65–0.76		
Median year of OC diagnosis post-2000	1.18	1.06–1.31		

Continued

Table 23.1 Continued

Parity			Fortner et al. [88]	2015
Full-term pregnancy	0.73	0.58–0.92		
Borderline	1.12	0.59–2.13		
Type I invasive epithelial ovarian cancer	0.47	0.33–0.69		
Type II invasive epithelial ovarian cancer	0.81	0.61–1.06		
Parous	0.71	0.61–0.85	Yang et al. [89]	2012
Serous	0.83	0.65–1.06		
Endometrioid	0.49	0.30–0.80		
Mucinous	0.54	0.25–1.14		
Clear cell	0.28	0.13–0.62		
Other	0.76	0.56–1.04		
Breastfeeding			Fortner et al. [88]	2015
Borderline	1.02	0.54–1.93		
Type I	0.67	0.41–1.08		
Type II	0.85	0.64–1.13		
Infertility treatment			Jensen et al. [90]	2009
Gonadotrophins	0.83	0.50–1.37		
Clomifene	1.14	0.79–1.64		
Human chorionic gonadotrophin	0.89	0.62–1.29		
Gonadotrophin-releasing hormone	0.8	0.42–1.51		
Endometriosis			Pearce et al. [54]	2012
Low-grade serous	2.11	1.39–3.20		
Endometrioid	2.04	1.67–2.48		
Clear cell	3.05	2.43–3.84		
Obesity			Olsen et al. [46]	2013
Serous	0.98	0.94–1.02		
Low-grade serous	1.13	1.03–1.25		
Endometrioid	1.17	1.11–1.23		
Mucinous	1.19	1.06–1.32		
Borderline (serous)	1.24	1.18–1.30		

Continued

Table 23.1 Continued

Risk Factor	OR/RR	95% CI	Author	Year
Cigarette smoking			Faber et al. [47]	2013
Current				
Mucinous	1.13	1.03–1.65		
Borderline (mucinous)	1.83	1.39–2.41		
Former				
Borderline (serous)	1.3	1.12–1.50		
Hormone replacement therapy (HRT)	1.33	1.16–1.53	Yang et al. [89]	2012
Current users			Collaborative Group on Epidemiological Studies of Ovarian Cancer [48]	2015
<5 years duration	1.43	1.31–1.56		
≥5 years duration	1.41	1.34–1.49		
Past users (<5 years since last use)				
<5 years duration	1.17	0.97–1.38		
≥5 years duration	1.29	1.11–1.49		
Past users (≥5 years since last use)				
<5 years duration	0.94	0.88–1.02		
≥5 years duration	1.1	1.01–1.20		
Estradiol-only therapy (5 years or more)			Koskela-Niska et al. [49]	2013
Serous	1.45	1.20–1.75		
Mucinous	0.35	0.19–0.67		
Estradiol–progestin therapy (5 years or more)				
Sequential	1.35	1.20–1.63		
Sequential (endometrioid)	1.88	1.24–2.86		
Ever use			Fortner et al. [88]	2015
Borderline	0.62	0.33–1.03		
Type I	0.92	0.56–1.51		
Type II	1.12	0.85–1.48		

Continued

Table 23.1 Continued

Aspirin			Baandrup et al. [91]	2015
Low dose	0.94	0.85–1.05		
Low dose – long-term use (over 5 years)	0.77	0.55–1.08		
150 mg	0.82	0.68–0.99		
Statins	0.98	0.87–1.10	Baandrup et al. [53]	2015
Mucinous	0.63	0.39–1.00		

CI, confidence interval; OR, odds ratio; RR, risk ratio.

the reduction of OC risk associated with the OCP, with over 10 years' use associated with a 50% risk reduction. A stronger protective effect of the OCP has been found in women at high risk due to *BRCA1/2* mutations, and again the effect is proportional to duration of use.

Hysterectomy had for many years been thought to reduce the risk of OC. More recently, no evidence of an association between simple hysterectomy and ovarian cancer has been reported [41, 42] with an increased risk of OC with hysterectomy reported in women being diagnosed with OC after 2000 [43]. Although this temporal change is difficult to explain, it may possibly be due to a decrease in overall hysterectomy rates, move towards a vaginal rather than abdominal approach, decline in bilateral salpingo-oophorectomy performed at the same time, and increase in the age of those undergoing the procedure.

There is now observational population-based data that bilateral salpingectomy alone may be associated with a 42% (odds ratio [OR] 0.58; 95% confidence interval [CI] 0.36–0.95) decrease in ovarian cancer risk [44].

Lifestyle factors

A lot of work has been done to clarify the risk reduction of various lifestyle approaches, such as alcohol [45], obesity [46], cigarette smoking [47], and talc use. Some of these are subtype specific, such as endometriosis, cigarette smoking, and obesity, while others are 'general risk factors'. Use of talc in the genital area has consistently been shown to increase the risk of OC and therefore it is not recommended.

Drugs

Hormone replacement therapy

Data from the observational studies show an increased risk of OC with hormone replacement therapy (HRT) use. An individual participant meta-analysis of 52 epidemiological studies reported that women who use hormone therapy for five years from around age 50 have about one extra ovarian cancer per 1000 users [48]. Estradiol-only therapy (if used for five years or more) increases the risk

of serous OC by 45%, but decreases the risk of mucinous OC by 65%, while estradiol–progestin therapy (five years or more), if used as a sequential regimen, increases the risk by 35% compared to the continuous regimen, which did not (Table 23.1) [49].

Aspirin

More recently, low-dose aspirin has been shown to be associated with a reduction of ovarian [50] and endometrial cancer [51] risk in the general population. There is emerging evidence of risk reduction of ovarian and endometrial cancers in high-risk women with Lynch syndrome as well [52].

Statins

Limited data indicate a decreased risk of ovarian cancer among those using statins. Recently, a large Danish nationwide study of 4103 cases and 58 706 controls reported a neutral association between ever using statins and OC risk (OR 0.98, 95% CI 0.87–1.10) [53].

Other risk factors

Women with endometriosis are at an increased risk of epithelial OC. An analysis of 13 ovarian cancer case-control studies from the Ovarian Cancer Association Consortium has shown that women who self-reported endometriosis were substantially more likely to develop clear-cell (OR 3.05, 95% CI 2.43–3.84), low-grade serous (OR 2.11, 95% CI 1.39–3.20), and invasive endometrioid ovarian cancers (OR 2.04, 95% CI 1.67–2.48) [54]. There was no association between endometriosis and risk of mucinous or high-grade serous invasive epithelial OC or borderline tumours of either subtype. Risk related to endometriosis was less pronounced in multiparous women compared to nulliparous, again suggesting the protective effect of parity.

Recent evidence indicates that endometriosis-associated OC shows favourable characteristics, including low-grade and early-stage disease. But it is unlikely that the presence of endometriosis affects disease progression after the onset of OC. Consequently, in those with a diagnosis of endometriosis, timely treatment may be advisable to reduce the OC risk.

Risk-prediction models

Significant efforts are under way to improve risk prediction. There are several predictive models that use family history to estimate mutation risk in *BRCA* genes and lifetime risk of OC, such as BRCAPRO, BODICEA, and Myriad II, as well as the Finnish, US National Cancer Institute, University of Pennsylvania, and Yale University models [55]. Although each model is unique based on the methods/population used, their performances in identifying women who have a high probability of carrying a *BRCA1/2* mutation have similar discrimination ability, ranging from 71% (Yale) to 83% (BRCAPRO) [56]. Such models may prove as useful tools

to assess cancer risk on a population basis in the future. Major efforts are now under way to further improve prediction using a combination of genetic and epidemiological factors. It is likely that in the future risks of a lower magnitude (<10% lifetime risk of OC) may instigate consultations between women and their gynaecologists [3].

Prevention

In the context of OC, all strategies available reduce risk but do not completely eliminate the possibility of a cancer arising in the future.

Risk-reducing surgery

Risk-reducing salpingo-oophorectomy (RRSO) reduces ovarian cancer risk in *BRCA* mutation carriers by 85% [57]. It is associated with a relatively low complication rate (3.9%; 95% CI 2.0–6.7%) [5]. RRSO is routinely recommended in high-risk women after completion of their families. While the standard recommendation is from the age of 35, it is important to individualize this, especially in women with *BRCA2* gene mutations. In Lynch syndrome women, the risk-reducing surgery includes hysterectomy. Removal of the ovaries leads to premature menopause, which is associated with increased morbidity and mortality, and hence RRSO is usually accompanied by use of HRT till the age of natural menopause [58]. Based on emerging evidence that most high-grade serous ovarian cancers originate in the fallopian tubes and involve the ovary secondarily [59], removal of the tubes alone has been put forward as an alternative risk-reducing strategy. McAlpine et al. [60] have already reported on the uptake, risk, and complications of opportunistic salpingectomy. This has been widely implemented in women undergoing pelvic surgery in Canada and endorsed by the Society of Gynecologic Oncology in the USA [61]. Gynaecologists surveyed in the UK have indicated that they would be willing to undertake bilateral salpingectomy at the time of hysterectomy (92%) or tubal ligation (65%) [62]. More recently, an approach based on bilateral salpingectomy with delayed oophorectomy in BRCA mutation carriers is being trialed in the United States [63]. Similar trial is to launch in the United Kingdom.

Aspirin

In the CAPP2 randomized controlled trial (RCT) of Lynch syndrome women, aspirin (600 mg a day for at least two years) reduced the risk of colorectal cancer (hazard ratio [HR] 0.63, 95% CI 0.35–1.13, p=0.12), with a similar effect on other noncolorectal Lynch syndrome cancers (HR 0.63, 95% CI 0.34–1.19, p=0.16) [52]. Hence it is increasingly applied (with some women using a 75 mg low-dose regime) to reduce the risk of ovarian and endometrial cancer in these women. The current trial (CaPP3) [64] due to report in 2020 is assessing the lowest dose (100, 300, and 600 mg per day) that confers such risk reduction in these women.

Oral contraceptive pill

Due to side effects, it is not currently recommended that women, especially those in their 40s, take OCP solely for OC risk reduction. That is, however, an added advantage, especially in those at high risk, who are considering using OCP for contraception or other medical indications.

Screening for ovarian cancer

Currently, there is no screening programme for ovarian cancer. In 2012, the US Preventative Task Force (USPSTF) reaffirmed its previous recommendation that screening should not be undertaken in the general population [65]. The National Institute for Health and Clinical Excellence (NICE) guidance in the UK advises that investigations should be carried out in women (especially if 50 years or over) only if reporting persistent or frequent symptoms (abdominal distension, early satiety, loss of appetite, pelvic or abdominal pain, or increased urinary urgency and/or frequency), particularly if more than 12 times per month [66]. However, recent evidence from the UK trial suggests that annual screening in the general population using a multimodal approach may be associated with a mortality benefit, which needs to be confirmed on further follow-up [67].

General population

In view of the improved survival in OC patients detected at an early stage, and the fact that a screening strategy based on CA125 and ultrasound demonstrated survival advantage in the screened women, large RCTs of OC screening were set up in the mid-1990s. The results of the ovarian arm of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, an RCT where 30 630 women aged 55–74 between 1993 and 2007 underwent screening using serum CA125 with a cut-off of ≥35 kU/l and transvaginal ultrasound (TVS) for four years, followed by CA125 alone for a further two years, showed no mortality benefit (mortality rate ratio 1.18, 95% CI 0.91–1.54) at a median follow-up of 12.4 years. Moreover, there was a high (15%) serious complication rate in women undergoing surgery for false-positive findings [68]. Updated data based on extended follow up at median of 14.7 years re-confirmed the lack of mortality benefit [69].

More encouraging data from the Kentucky single-arm ultrasound study of 37 293 women (a mean follow up of 5.8 years) found five-year survival rates in women with primary invasive epithelial cancer who were screened to be significantly higher (74.8% ± 6.6%) compared to unscreened nonstudy women (53.7% ± 2.3%) [70]. However, these rates are not comparable due to the 'lead-time effect' of screening and the likelihood of a significant healthy volunteer effect in those who participated in the screening study [71].

The largest RCT to date is the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), in which 202 638 women from the general population

were randomized to no intervention (control) or annual screening using either transvaginal ultrasound (USS, n=50 639) or serum CA125 interpreted using the 'Risk of Ovarian Cancer' algorithm (ROCA), with transvaginal ultrasound as a second-line test (multimodal screening, MMS, n=50 640). Screening was completed at the end of 2011. On the prevalence screen, both MMS and USS strategies had encouraging sensitivity for primary invasive epithelial ovarian/tubal cancers (iEOC; 89.5% and 75%, respectively) [72]. During incidence screening in the MMS arm, sensitivity and specificity of the multimodal strategy for iEOC was 86%, with 4.8 women undergoing surgery/detected iEOC. The ROCA assigns risk of ovarian cancer based on age and CA125 profile. Interpreting the annual serum CA125 using the ROCA detected 86.5% (134/155) of iEOC diagnosed within one year of the screen, while an approach using fixed CA125 cut-off at the last annual screen of >35, >30, or >22U/mL would have identified 41.3%, 48.4%, and 66.5%, respectively. The area under the curve for ROCA (0.915) was significantly (p=0.0027) higher than for a single threshold rule (0.869), with screening using ROCA doubling the number of screen-detected iEOCs compared to a fixed cut-off [73]. Independent validation of the UK findings of high specificity and positive predictive value of ROCA was reported from a single-arm US prospective study of 4051 low-risk postmenopausal women [74].

Mortality outcome data from UKCTOCS based on follow-up until 31 December 2014 suggests that screening using the multimodal strategy may result in a reduction in ovarian cancer mortality [67]. There was a significant stage shift of iEOC and primary peritoneal cancers in the MMS arm (36.1% Stage I/II) compared to control (23.9% Stage I/II). The reduction in ovarian and tubal cancer deaths (MMS 15%; USS 11%) over 14 years was not significant in the primary Cox analysis comparing either group to control. However, this overall estimate comprised a reduction of 8% in the first seven years of the trial and 23% in years 7–14 in the MMS group, and 2% and 21%, respectively, in the USS group. This delayed mortality effect of screening was similar to that seen in other screening trials, and was associated with a significant (p=0.023) mortality reduction in the MMS versus control comparison, using the weighted log-rank analysis adopted by the PLCO trialists. A significant (p=0.021) mortality reduction of 20% was also observed in the MMS group when the prevalent cases (women who had OC prior to the start of trial) were excluded from the analysis. The mortality reductions in the USS arm were not significant. With regard to harms, per 10 000 screens, 14 women in the MMS arm and 50 in the USS arm underwent trial surgery as a result of positive screen results and were then found to have only benign ovarian lesions or normal ovaries. The major surgical complication rate in the latter was low (3.1% MMS and 3.5% USS) and similar to those usually reported for such surgery. The initial cost-effectiveness analysis demonstrated that the MMS strategy falls within the NICE threshold [75]. Further follow up for four years is currently underway before firm conclusions on the efficacy and cost-effectiveness of screening can be reached.

High risk

Annual screening for OC is not recommended in high-risk women, as it is not effective in detecting early-stage disease [76]. A shorter screening interval of four months using serum CA125 interpreted by ROCA and transvaginal ultrasound was investigated in the UK Familial Ovarian Cancer Screening Study (UKFOCSS) Phase II. Such intensive screening will lead to women recalled for abnormal results experiencing transient cancer-specific distress, but there was no significant effect on general anxiety/depression or overall reassurance [77].

The results of Phase II demonstrate a significant stage shift in women diagnosed with invasive epithelial ovarian, tubal and peritoneal cancers within 1 year of last screen (63% Stage I-IIIA) compared with those diagnosed >1 year after screening ended (6% Stage I-IIIA; p=0.0004). Moreover, there were higher rates of zero residual disease after debulking (95% versus 72%; p=0.09) and lower rates of neoadjuvant chemotherapy (5% versus 44%; p=0.008) in those detected within a year of the last screen [78]. The performance of a similar strategy using ROCA has been evaluated prospectively in screening trials in women at high risk in the USA (Cancer Genetics Network, CGN, and Gynaecology Oncology Group, GOG) and reported similar stage shift [79].

There are currently differing views on whether screening should be offered to high-risk women. In the UK in the NHS there is no screening for OC in high-risk women, with risk management confined to RRSO and symptom awareness. However, in the USA, while the primary recommendation is risk-reducing surgery, the US National Comprehensive Cancer Network guidelines consider six-monthly screening using serum CA125 and TVS a reasonable approach for those who do not wish to undergo surgery.

Future directions

The goal is to develop a new generation of screening tests based on tumour DNA [80], in view of the recent emerging evidence that TP53 mutations could be detected in vaginal sections of 60% of patients with high-grade serous cancer, and novel specimens such as cervical samples [81]. More recently, a multi-analyte test (CancerSEEK) of eight biomarkers including CA125 and TP53 mutations exhibited a high sensitivity of 98% for ovarian cancer [82].

Symptom awareness

Symptoms for ovarian cancer, albeit nonspecific, are not 'silent', but may lead to earlier diagnosis with less tumour burden [83]. In the UK, NICE issued guidelines in 2011 stating that any women (especially those over 50) presenting to primary care with persistent abdominal distension/'bloating', feeling full and/or loss of appetite, pelvic/abdominal pain, increased urinary urgency and/or frequency, unexplained weight loss, fatigue, or changes in bowel habit should have a CA125 test followed by TVS. However, during the NHS campaign 'Be Clear on Cancer',

the high prevalence (14% of those over 45 years presenting to primary care had frequent and/or severe symptoms) of these gynaecological cancer symptoms has become evident [84]. Use of public awareness campaigns is probably best aimed at those at high risk, as otherwise the burden in increase in consultation could be unmanageable.

Conclusion

There is a significant effort under way to identify epidemiological and genetic risk factors for ovarian cancer and improve on the current risk-prediction models so that prevention and screening can be tailored to the individual. In high-risk women, RRSO following completion of the family is recommended. There is an increasing trend to recommend low-dose aspirin to women with Lynch syndrome. There is good evidence that multimodal screening using serum CA125 interpreted using ROCA with TVS as a second-line test has the best performance characteristics to date. Recent data from UKCTOCS suggest that annual multimodal screening may be associated with a mortality benefit in the general population, with estimates of mortality reduction of around 20%. Further follow-up is required to confirm the effect size and the cost-effectiveness before any general population screening is considered. Recommendations for high-risk women who decide not to undergo RRSO are controversial. Whilst 4-monthly screening using ROCA demonstrated significant stage shift, screening is currently not available on the NHS in the UK, but is recommended six-monthly in the USA. In the meantime, major efforts are in progress to explore preventive strategies such as opportunistic bilateral salpingectomy in both the low- and high-risk populations, and to develop a new generation of screening tests based on tumour DNA and novel specimens such as cervical samples.

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Exhibit 128

Epithelial ovarian cancer

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Epithelial ovarian cancer generally presents at an advanced stage and is the most common cause of gynaecological cancer death. Treatment requires expert multidisciplinary care. Population-based screening has been ineffective, but new approaches for early diagnosis and prevention that leverage molecular genomics are in development. Initial therapy includes surgery and adjuvant therapy. Epithelial ovarian cancer is composed of distinct histological subtypes with unique genomic characteristics, which are improving the precision and effectiveness of therapy, allowing discovery of predictors of response such as mutations in breast cancer susceptibility genes *BRCA1* and *BRCA2*, and homologous recombination deficiency for DNA damage response pathway inhibitors or resistance (cyclin E1). Rapidly evolving techniques to measure genomic changes in tumour and blood allow for assessment of sensitivity and emergence of resistance to therapy, and might be accurate indicators of residual disease. Recurrence is usually incurable, and patient symptom control and quality of life are key considerations at this stage. Treatments for recurrence have to be designed from a patient's perspective and incorporate meaningful measures of benefit. Urgent progress is needed to develop evidence and consensus-based treatment guidelines for each subgroup, and requires close international cooperation in conducting clinical trials through academic research groups such as the Gynecologic Cancer Intergroup.

Epidemiology and risk factors

Since the last seminar publication 4 years ago,[1] there have been major improvements in the understanding of the biology of invasive epithelial ovarian cancer (EOC) (figure 1), and this knowledge has led to changes in clinical practice. This Seminar will summarise the current optimal evidence-based approach to management of EOC. EOC is the most lethal gynaecological cancer. Annually worldwide, 230 000 women will be diagnosed and 150 000 will die.[2] It represents the seventh most commonly diagnosed cancer among women in the world with 46% survival 5 years after the diagnosis.[3] One of the main factors contributing to the high death-to-incidence rate is the advanced stage of the disease at the time of diagnosis. Late stage presentation has a 5-year relative survival rate of 29%, by contrast with 92% for early-stage disease.[4] About 75% of patients are diagnosed at an advanced stage because of the asymptomatic nature of EOC. Genomic predisposition to EOC is now well recognised in up to 15% of affected women. Breast cancer susceptibility genes *BRCA1* and *BRCA2* have been identified as causative genes involved in 65–75% of hereditary EOC. Deleterious mutations in *BRCA1* and *BRCA2,* and other double-strand DNA break repair genes, are largely associated with the high-grade serous EOC subtype susceptibility. Lynch syndrome, an autosomal dominant hereditary cancer family syndrome, accounts for 10–15% of hereditary EOC,[5,6] and is typically associated with endometrioid or clear-cell tumours.[4] Other genetic syndromes include Peutz-Jegher and rare disorders, such as Gorlin syndrome.[7] Risk factors for EOC include the number of lifetime ovulations (absence of pregnancy, early age of menarche, and late age at menopause), family history of EOC, smoking, benign gynaecological conditions (including endometriosis, polycystic ovary syndrome, and pelvic inflammatory disease),[4] and potentially use of talcum powder.[8]

Screening

Considerable efforts have been made to implement screening of the general population to diagnose EOC early, but there is no approved strategy.[9] The UKCTOCS trial (NCT00058032), a randomised controlled trial of over 200 000 women assessing annual multimodal screening with serum cancer antigen (CA125), did not identify significant mortality reduction when the risk for ovarian cancer algorithm (ROCA) was used, versus annual transvaginal ultrasound screening, versus no screening. Further follow-up is underway to assess late benefit (7–14 years after an index screening event) in post-menopausal women because of a significant stage shift in women diagnosed with invasive ovarian, tubal, or peritoneal cancer with multimodal screening compared to no screening.[10] Additional biomarker combinations such as human epididymis protein 4, a glycoprotein secreted by the Mullerian epithelia of the female reproductive tract, have been tested with CA125,[11] but further studies are required. A study[12] screened 4348 women with 10% or higher lifetime risk of ovarian or fallopian tube cancer using ROCA and transvaginal sonography, showing evidence for stage shift, with 53% of diagnoses made during the trial being early-stage cancers, compared with only 6% of early-stage cancers detected more than 1 year after the trial screening finished. Longer follow-up will determine the effect of this strategy on survival. The recommendation for unaffected individuals with a high familial risk of ovarian cancer is risk-reducing salpingo-oophorectomy by an age that depends on their individual genetic predisposition. Efforts are also underway to improve genomic screening strategy.[13]

Diagnosis

EOC symptoms are not specific and include abdominal bloating, early satiety, nausea, abdominal distension, change in bowel function, urinary symptoms, back pain, fatigue, and loss of weight, which typically present months

before diagnosis.[14] Initial investigations include the measurement of CA125 concentrations and pelvic ultrasound. To accurately define EOC extension, further imaging should include chest and abdomen or pelvis CTs for staging, and potentially a pelvic MRI. Optimal staging is surgical and includes total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, inspection of peritoneal surfaces with biopsy or removal of any suspicious areas, and para-aortic and pelvic lymph node dissection. Surgery should be done by a trained gynaecological oncology surgeon with the goal of no residual disease. The staging procedure will establish the surgical stage, conventionally with International Federation of Gynecology and Obstetrics (FIGO) staging of ovarian cancer or with tumour, node, metastasis classifications by the American Joint Committee on Cancer.[15,16]

Pathological diagnosis on tumour tissue is essential because ovarian cancer has different histological subtypes with different treatment approaches. Over the past decade it has become clear that EOC consists of a number of diseases (figure 2) with distinct precursor lesions, tissues of origin, molecular biology, clinical presentation, chemosensitivity, and patient outcome.

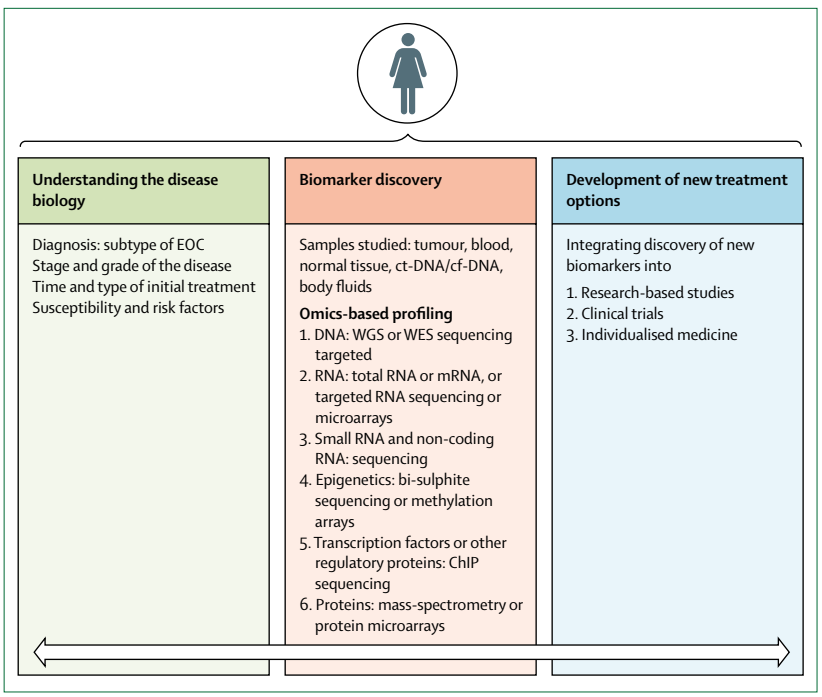

Figure 1: **Evolving management strategies based on disease biology and molecular profiling of novel biospecimens**
Integrated approach combining understanding of ovarian cancer disease biology and evolution, and application of novel omics-based technologies as a part of research-based studies or clinical trials. EOC=epithelial ovarian cancer. ct-DNA=circulating tumour DNA. cf-DNA=circulating free DNA. WGS=whole genome sequencing. WES=whole exome sequencing. ChIP=chromatin immunoprecipitation.

First-line treatment approach

Surgery

Primary debulking surgery (PDS) followed by chemotherapy has become the standard of care in advanced EOC since the 1980s, despite few upfront randomised trials defining its actual benefit.[17] No residual tumour (R0) after PDS is the most important prognostic factor for survival.[18] Two randomised clinical trials comparing PDS and chemotherapy with neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) showed similar survival with a low operative morbidity when NACT and IDS were used.[19,20] Both trials have been criticised for their low R0 rates and low survival rates. However, it should be noted that most of the patients had extensive stage IIIC or IV disease. To help the debate, the TRUST trial (NCT02828618) randomising NACT versus PDS in advanced EOC is ongoing in selected centres with 50% or more R0 rates and the results will be available in a few years. The choice between PDS and chemotherapy or NACT and IDS is controversial.[21] Further research is needed on how to select patients for PDS or NACT, including better and validated imaging or laparoscopic scoring systems and algorithms to predict operative morbidity.

A guideline for selecting patients with FIGO stage IIIC and IV disease for PDS or NACT followed by IDS is presented in the table.[22] The algorithm and guideline are based on the EORTC 55971 randomised trial,[20] showing that patients with stage IIIC disease and small metastases (<5 cm) had better overall survival with PDS whereas patients with stage IV disease had better survival with NACT. At the time of surgery, all visible or palpable tumour must be removed at PDS and IDS.[18,20] For decades the role of a full pelvic and para-aortic lymphadenectomy in advanced EOC has been advocated.[25] However, a randomised study from the AGO-OVAR trial,[26] has shown that systematic pelvic and para-aortic lymphadenectomy in patients with advanced EOC with both intra-abdominal complete resection and clinically negative lymph nodes does not improve overall or progression-free survival (PFS).

In patients with stage IA low grade disease opting for fertility conservation surgery, the uterus and contralateral ovary can be left in place pending pathology review of the removed tissues and further discussion with the patient. The selection of patients for fertility preservation requires very careful consideration of the risks and benefits between the surgical oncologist and patient. The likelihood of cure is high for women with stage IA disease, but residual disease and subsequent recurrence are associated with low likelihood of salvage. Pathological differences greatly affect the potential for conservative surgery, and this option is best reserved for women with well-differentiated or low-grade, stage IA disease.[27]

Systemic therapy

The treatment guidelines for EOC have largely been driven by high grade serous ovarian cancer (HGSOC), and first-line therapy has largely been established on the basis of this subgroup. Randomised clinical trials in early-stage disease have been challenging to do because

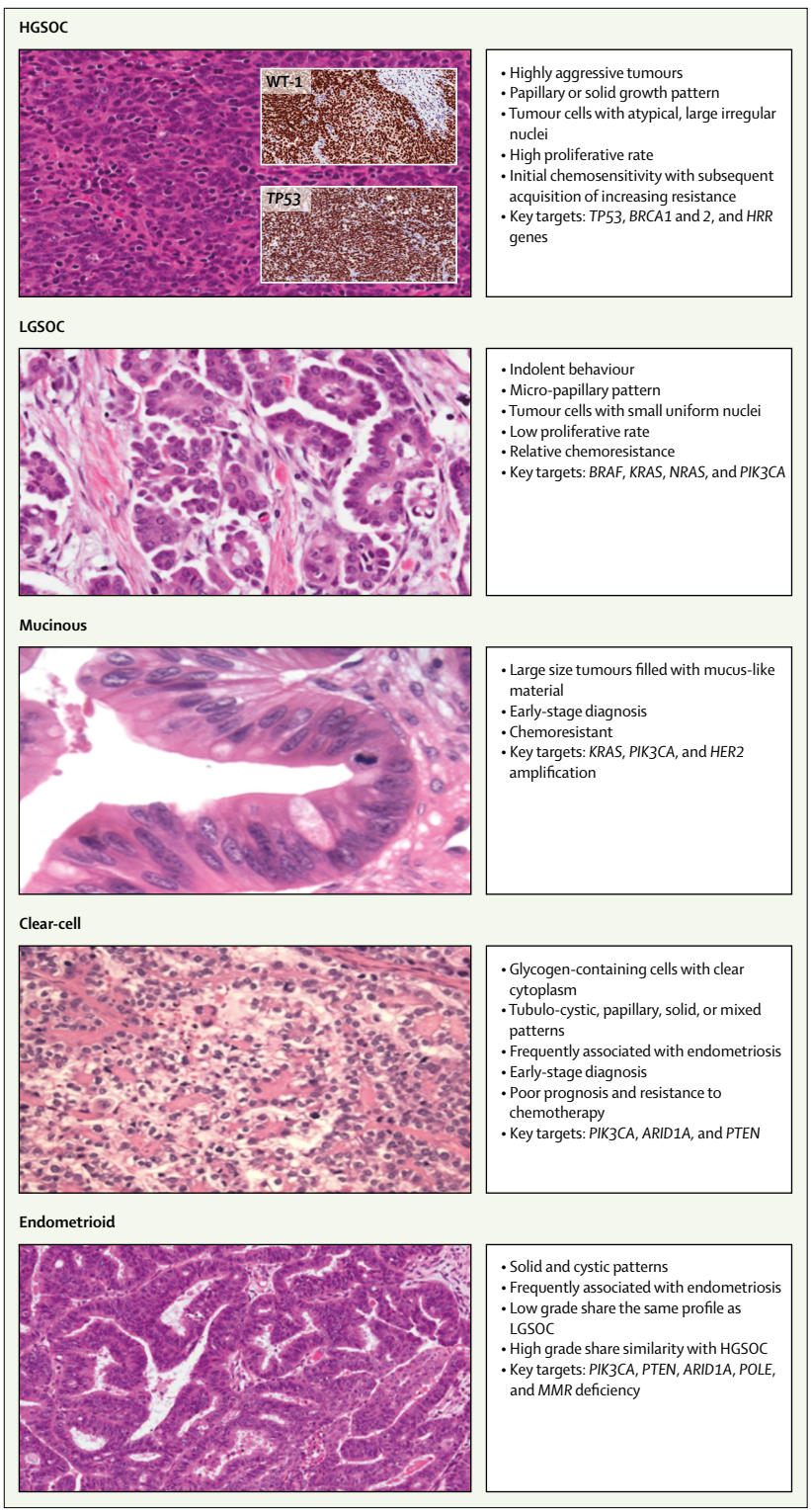

Figure 2: **Different histological subtypes of epithelial ovarian cancers and their salient features**
P53 and WT1 staining in HGSOC is shown. The magnifications for H and E range between 50–400×, whereas immunohistochemistry is 50×. HGSOC=high-grade serous ovarian carcinoma. LGSOC=low-grade serous ovarian carcinoma.

a minority of patients present early. The ICON[28] and ACTION[29] randomised trials support the use of adjuvant chemotherapy in early-stage disease, with carboplatin or cisplatin and paclitaxel, with level Ia evidence.[28–33] Subset analyses raised the question of avoiding chemotherapy in well-staged patients with early-stage disease, but this finding should be considered as exploratory.[34] The question of adjuvant therapy for early-stage disease can be discussed on the basis of histology subtype and grade.[35] The GOG157 trial[36] compared three versus six cycles of adjuvant paclitaxel and carboplatin, but was powered to detect a 50% decrease in the recurrence rate at 5 years; there was no difference in the groups, perhaps supporting a reduction in the number of cycles, with reduced toxicity in well-staged patients. However, the standard recommendation in practice is six cycles of platinum adjuvant therapy.

Intravenous administration of carboplatin (area under the curve 5–6) and paclitaxel (175 mg/m² over 3 h) every 3 weeks is the standard first-line chemotherapy drug treatment for advanced-stage EOC.[37] Weekly intravenous paclitaxel administration has been investigated and might be an alternative to paclitaxel in combination with intravenous carboplatin administrated once every 3 weeks. In the Japanese Gynecologic Oncology Group 3016 study, 631 women with stage II–IV EOC were randomised between carboplatin AUC 6 with paclitaxel 180 mg/m² every 3 weeks, and carboplatin AUC 6 every 3 weeks with weekly paclitaxel 80 mg/m². A sustained significant improvement in PFS and overall survival for patients receiving dose-dense therapy compared with conventional treatment was reported.[38] However, a benefit in PFS was not seen in three other trials with weekly paclitaxel,[39–41] possibly because of pharmacogenomic influences because the initial JGOG 3016 trial[38] (NCT00226915) was in a Japanese population whereas the subsequent trials[39–41] were predominantly in white populations.

Two randomised trials, GOG218[42] and ICON7,[43] showed a significantly increased PFS, but not overall survival with the addition of the anti-angiogenesis inhibitor bevacizumab (directed against vascular endothelial growth factor), to paclitaxel every 3 weeks and carboplatin followed by maintenance bevacizumab. In a pre-planned analysis of the ICON7 study,[43] the addition of bevacizumab in women at high risk of progression (stage III disease with >1 cm residual disease following PDS, and inoperable patients with stage III and IV disease), significantly improved the estimated median PFS (10·5 months with standard therapy *vs* 15·9 months with bevacizumab [hazard ratio (HR) 0·68; 95% CI, 0·55–0·85; p<0·001] and median overall survival (28·8 *vs* 36·6 months [0·64; 0·48–0·85; p=0·002]). These findings led to the addition of bevacizumab to paclitaxel and carboplatin every 3 weeks as standard of care in this high-risk population in many countries. The AGO trials group exploring 15 versus 30 cycles of chemotherapy[44–46] will confirm

	Both Leuven and Essen criteria	Essen criteria only	Leuven criteria only
Diagnosis	Biopsy with histologically proven epithelial ovarian, tubal or peritoneal cancer FIGO stage IIIC-IV	..	Fine needle aspiration proving the presence of carcinoma cells in patients with a suspicious pelvic mass if CA125 (KU/L)/CEA (ng/mL) ratio is >25; if the serum CA125/CEA ratio is ≤25, imaging or endoscopy is obligatory to exclude a primary gastric, colon, or breast carcinoma
Abdominal metastases	Involvement of the superior mesenteric artery; diffuse deep infiltration of the root of the small bowel; diffuse and confluent carcinomatosis of the stomach or small bowel involving such large parts that resection would lead to a short bowel syndrome or a total gastrectomy	Multiple parenchymatous liver metastases in both lobes; tumour involving large parts of the pancreas (not limited to tail) or the duodenum or both; tumour infiltrating the vessels of the ligamentum hepatoduodenale or truncus coeliacus	Intrahepatic metastases; infiltration of the duodenum or pancreas, or the large vessels of the ligamentum hepatoduodenale, truncus coeliacus, or behind the porta hepatis
Extra-abdominal metastases	..	Not fully resectable metastases (eg, multiple parenchymal lung metastases*, non-resectable lymph node metastases, and brain metastases)	All excluding: resectable inguinal lymph nodes, solitary resectable retrocrual or paracardial nodes, and pleural fluid containing cytologically malignant cells without proof of the presence of pleural tumours
Patients' characteristics	Impaired performance status and comorbidity not allowing a maximal surgical effort to achieve a complete resection; patients' non-acceptance of potential supportive measures such as blood transfusions or temporary stoma	..	..
Criteria for interval debulking	..	Upfront surgical effort in an institution without specialised expert availability, surgical skills competency, and adequate infrastructure; barrier for initial surgery has disappeared (eg, improved medical condition); interval debulking is not indicated, if the reason for primary chemotherapy was tumour growth pattern, diagnosed during open surgery by an experienced gynaecological oncologist under optimal circumstances (as in GOG study 152[23])	No progressive disease, and in case of extra-abdominal disease at diagnosis the extra-abdominal disease should be in complete response to treatment or resectable; performance status and comorbidity allowing a maximal surgical effort resulting in no residual diseases

Adapted with permission from Vergote I, et al.[24] FIGO=International Federation of Gynaecology and Obstetrics. *Preferably histologically proven.

Table: **Leuven and Essen criteria for considering neoadjuvant chemotherapy and interval debulking surgery in FIGO stage IIIC and IV ovarian carcinoma**

or refute the hypothesis from the ICON7[43] and ROSIA[44] trials that benefit of bevacizumab is related to the maintenance duration.

The use of intraperitoneal cisplatin and paclitaxel has resulted in a survival advantage in several trials in patients with less than 1 cm residual tumour after PDS.[47–49] These trials have been criticised because they were hampered by outdated control groups, experimental intraperitoneal chemotherapy groups, various changes (eg, different dose, dose-dense regimens), and higher toxicity.[50] The role of intraperitoneal therapy has come into question with the GOG252 study, assessing dose-dense intravenous treatment versus intraperitoneal therapy with the addition of bevacizumab, of which intraperitoneal therapy with bevacizumab did not show any benefit in PFS for patients with FIGO stage 3 disease and less than 1 cm residual tumour following PDS.[51] These findings seem to show that dose for dose, there is no advantage of intraperitoneal chemotherapy over intravenous chemotherapy. Studies that were associated with benefit of intraperitoneal chemotherapy used intraperitoneal cisplatin at 100 mg/m² and were associated with a higher incidence of toxicity.

Hyperthermic intraperitoneal chemotherapy (HIPEC) until 2017 had no proven benefit in EOC.[52] However, in 2017, two randomised studies from Dutch[53] and Korean[54] groups used HIPEC at the time of IDS after NACT.[52–54] The Dutch trial reported significant advantage for the HIPEC group, which was not observed in the Korean trial. In the Dutch trial, the median recurrence-free survival was 10·7 months in the surgery group and 14·2 months in the surgery with HIPEC group, and the median overall survival was 33·9 months in the surgery group versus 45·7 months in the surgery with HIPEC group. In women who received NACT in the Korean trial, the median PFS was 20 months for the HIPEC group and 19 months for the control group (log-rank test, p=0·137), and the median overall survival was 54 months for the HIPEC group and 51 months for the control group (log-rank test, p=0·407). These trials were small and resulted in higher toxicity when HIPEC was used, and should be confirmed before HIPEC can be used as standard of care.[55] The key question of whether benefit is related to an additional intraperitoneal cycle of therapy or the potential association with hyperthermia is going to be evaluated in a prospective trial (Dr Sudeep Gupta, Tata Memorial Centre, Mumbai, personal communication).

Follow-up

Follow-up might identify disease recurrence earlier, but there are no clear guidelines on the type and frequency; regular physical examination is generally recommended. The earliest indication of recurrent disease might be CA125 in patients where this has been a marker of disease. With neither radiological nor clinical evidence of disease, recurrence can be defined by the rise of more

than twice the upper limit of normal (ULN is 35 U/mL) for patients with normal baseline CA125 levels, or for those whose CA125 levels have normalised during treatment, or CA125 level more than twice nadir value (on two successive occasions) for patients whose CA125 levels have not normalised. The question of value from close monitoring to detect recurrence early remains, because no survival benefit was observed with early treatment of relapse on the basis of increased CA125 alone.[56] This finding might have been because of the paucity of effective therapeutic options at recurrence, or a limitation of the study, which was underpowered to detect a potential survival benefit in patients eligible for secondary cytoreduction. Although early detection might not have survival advantage, it does allow for exploration of treatment options, including surgery or experimental therapies, which have led to regular follow-up after completion of primary therapy.

See Online for appendix

CT scans can detect an asymptomatic recurrence and should be systematically done to establish a baseline before starting new lines of therapy. Several studies have demonstrated the use of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET and ^{18}F-FDG PET integrated with CT for early detection of recurrent EOC, and MRI in the evaluation of patients with recurrent EOC and its potential role of prediction of optimal secondary debulking surgery (SDS).[57]

Recurrence

Recurrence is incurable in about 75% of women who present with advanced disease. A functional algorithm using the platinum-free interval to select subsequent therapy has been a simple and remarkably effective way of choosing therapy and inferring prognosis for the last 30 years. In November, 2015, the Gynecologic Cancer Intergroup redefined the conventional practice of using platinum-free interval to categorise patients as platinum-sensitive or platinum-resistant, and replaced this practice by a therapy-free interval, with the cutoff at 6 months.[58]

At the time of relapse, SDS should be considered for appropriate patients.[59] AGO-OVAR developed the Descriptive Evaluation of preoperative Selection KriTeria for OPerability (DESKTOP) score as a predictive algorithm of effective SDS.[60] Patients with the first recurrence and a platinum-free interval of more than 6 months (platinum-sensitive) EOC have a positive DESKTOP score when accompanied by good performance status (Eastern Cooperative Oncology Group [ECOG] scale 0), complete resection during first-line therapy, and ascites of less than 500 mL; these patients have a significantly better PFS when undergoing SDS followed by chemotherapy, versus chemotherapy alone.[61] A positive DESKTOP score predicted the probability of complete resection in more than two out of three patients with 95% accuracy.[60] The Tian Risk model,[62] which is also based on the factors affecting the SDS surgical outcome, utilises six factors predicting complete cytoreduction: FIGO stage (I and II *vs* III and IV), residual disease after primary cytoreduction (0 mm *vs* >0 mm), PFS (<16 months *vs* ≥16 months), ECOG performance status (0–1 *vs* 2–3), CA125 (≤ 105 U/mL *vs* >105 U/mL), and ascites at recurrence (absent *vs* present). Memorial Sloan Kettering criteria are also used to predict for complete gross resection in secondary cytoreductive surgery in EOC.[63]

If there is no surgical option, systemic therapy is used to control the disease for as long as possible. Several clinical trials have changed the options for care and remain an active area of investigation to overcome systemic therapy resistance. The type of treatment will be based on patient, time of recurrence, tumour histology, and disease biology. Given that HGSOC is the most common type of EOC, we will focus on this specific group. The other histology subtypes including low-grade serous, clear-cell, endometrioid, and mucinous are described in the appendix.

High grade serous ovarian cancer

Epidemiology and origin

HGSOC is the most common type of EOC, accounting for 75% of all EOC. HGSOC pathogenesis has evolved from the notion that it develops from the ovarian epithelium to the epithelium of the distal fallopian tube.[64] Serous tubal intraepithelial carcinomas are suspected to be the precursor lesion of some HGSOC, with molecular features involving mutations in *TP53* as an early event.[65] Bilateral salpingo oophorectomy is the standard of care for risk reduction in *BRCA1* and *BRCA2* carriers. Prevention studies are assessing bilateral salpingectomy with delayed oophorectomy in women with high risk.[66]

Hereditary susceptibility

As 15–20% of HGSOC patients have germline *BRCA1* or *BRCA2* mutations, diagnosis should trigger genetic testing.[67] The confirmation of germline mutation in a patient should also lead to offering germline testing offered to first degree relatives to identify carriers who might benefit from screening. In family predisposition studies, the cumulative risks of EOC by the age of 80 years are estimated to be 44% in *BRCA1* and 17% in *BRCA2* mutation carriers.[68] Female *BRCA1* or *BRCA2* mutation carriers should consider prophylactic risk-reduction surgery after childbearing and around age 38 years, when the risk of EOC begins to increase because this surgery is the only proven risk-reducing strategy.[69] Other genes of moderate penetrance involve *RAD51C, RAD51D,* and *BRIP1*; although their individual mutation frequency is uncommon (<1% each), cumulatively they might be responsible for about 5% of EOC. Therefore, genetic testing for women with HGSOC includes *BRCA1, BRCA2,* and other susceptibility genes.[70] Studies are also evaluating early detection of *TP53* in blood or uterine lavage as a potential genomic screen.[71,72]

Pathology

The growth pattern of HGSOC is heterogeneous, involving large papillae, being glandular, solid and occasionally micropapillary with frequent necrosis; it is defined by its high-grade nuclei and mitotic index[73] (figure 2). Immunohistochemistry stain is abnormal for p53, diffusely expressed for p16, and elevated for Ki67; additional markers include ER, PR, WT-1, and PAX8.

Molecular abnormality

HGSOC is characterised by gain of function mutations in *TP53*,[73] high-frequency somatic copy number alterations, and whole genome duplications.[74] HGSOC is associated with lower prevalence but recurrent somatic mutations in *NF1, BRCA1, BRCA2, RB1,* and *CDK12* [74] in around 5–8% of tumours (figure 3). HGSOC is also characterised with frequent DNA gains and losses, making this cancer chromosomally unstable, with potential for acquired chemoresistance (*CCNE1* amplification).[75] Heterozygous and homozygous loss is an important mechanism for inactivation of tumour suppressors.[76] Genomic analyses show that homologous recombination is defective in nearly half of HGSOC.[74] This homologous recombination deficiency (HRD) is a key determinant of platinum sensitivity in HGSOC and has been exploited for treatment with poly (ADP-ribose) polymerase inhibitors (PARPi).[77] Myriad HRD test and Foundation Medicine loss-of-heterozygosity assay assess HRD in tumours as a potential predictive biomarker for PARPi therapy. Molecularly, HGSOC might be stratified into four different prognostic subtypes (C1–mesenchymal, C2–immune, C4–differentiated, and C5–proliferative)[74,78,79] and potentially seven copy-number signatures;[80] both stratification methods require prospective validation to be used in a predictive way.

Treatment

In the platinum-sensitive recurrence setting, if surgery is not indicated, a re-challenge with platinum doublet chemotherapy is standard, with six to eight cycles of therapy.[81–84] Maintenance strategies have been developed to delay subsequent progression and possibly improve overall survival.[85] Phase 3 trials with bevacizumab showed a significant benefit for maintenance on disease control rate.[86,87] In the OCEANS trial,[86] the addition of bevacizumab to carboplatin and gemcitabine increased median PFS from 8·4 months to 12·4 months (HR 0·484; 95% CI, 0·388–0·605; log-rank p<0·0001). GOG213 confirmed the benefit of adding bevacizumab to carboplatin and paclitaxel with improvement in overall survival after correcting for platinum-free interval (0·823; 0·680–0·996; p=0·0447).[87]

A re-challenge with chemotherapy plus bevacizumab for platinum-sensitive recurrence and patients who previously received bevacizumab as first line showed a clinical benefit with a median PFS from 8·8 months to 11·8 months without and with bevacizumab, respectively (0·51, 0·41–0·64, p<0·001) but no significant difference in overall survival.[88] The benefit of adding and continuing an anti-angiogenic agent was further confirmed with cediranib.[89]

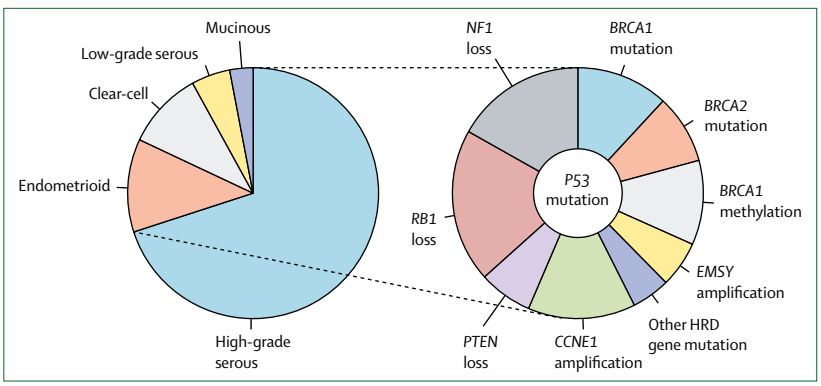

Figure 3: **Common molecular abnormalities in ovarian cancer**
Left side shows the breakdown of epithelial ovarian cancer according to histological subtype. Right side shows the breakdown of the main molecular abnormalities that are thought to drive high-grade serous ovarian tumours (*P53* mutation is an almost ubiquitous finding). *EMSY=EMSY, BRCA2* Interacting Transcriptional Repressor.

PARPi have been successfully implemented in recurrent HGSOC by leveraging inherent defects in DNA repair mechanisms present in around 50% of HGSOC because of mutations in *BRCA1, BRCA2,* or associated HRD genes, or by functional inactivation through methylation.[74] PARPi have shown remarkable activity as a single agent in women with recurrent disease regardless of *BRCA1* and *BRCA2* mutations, with improved activity in women with *BRCA1* or *BRCA2* mutations and platinum-sensitive disease.[90–93] Olaparib was the first PARPi approved initially for the treatment of advanced EOC in patients carrying germline *BRCA1* or *BRCA2* mutations who have received three or more previous lines of chemotherapy with response rate of 31·1% (95% CI 24·6–38·1).[91,94] In December, 2016, the US Food and Drug Administration (FDA) granted accelerated approval of rucaparib for the treatment of patients with HGSOC carrying deleterious germline or somatic *BRCA1* or *BRCA2* mutations previously treated with two or more lines of chemotherapy[92,95] on the basis of the investigator-assessed objective response rate of 54% (95% CI 44–64), and median duration of response of 9·2 months (6·6–11·7). Olaparib was approved in Europe as maintenance treatment in patients with platinum-sensitive relapsed HGSOC characterised by *BRCA1* or *BRCA2* mutations.[96] Among patients with a *BRCA1* and *BRCA2* mutation, median PFS was significantly longer in the olaparib group than in the placebo group (11·2 months [95% CI 8·3-not calculable] *vs* 4·3 months [3·0–5·4]; HR 0·18 [0·10–0·31]; p<0·0001); for patients with wild-type *BRCA1* and *BRCA2*, the difference was lower (7·4 months [5·5–10·3] *vs* 5·5 months [3·7–5·6]; HR 0·54 [0·34–0·85]; p=0·0075).[97] In women with *BRCA1* or *BRCA2* mutations, the SOLO2 trial[98] confirmed the importance

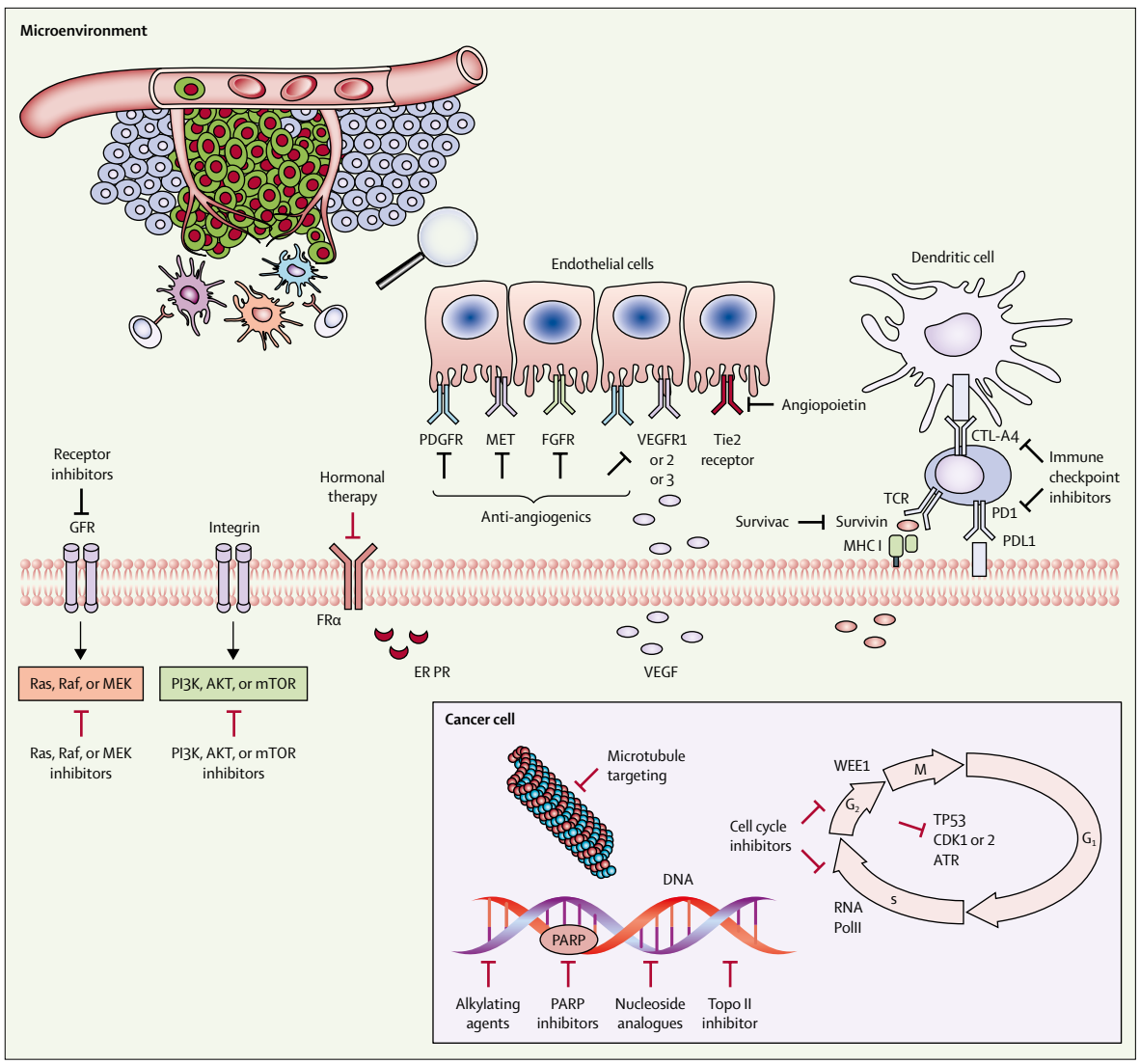

Figure 4: **Different molecular targets and pathways in ovarian cancers currently under investigation for drug development**
The molecular targets could arise from within a cancer cell or from the tumour microenvironment, such as host immune cells or vascular tissue.

of maintenance, which was followed by the FDA's approval of olaparib as maintenance therapy in women with platinum-sensitive disease following response to chemotherapy.

In December, 2018, the FDA approved olaparib for maintenance treatment of BRCA mutated advanced EOC following first-line platinum-based chemotherapy.[99] This approval was given on the basis of the SOLO1 trial[100] (70% lower risk of disease progression or death with olaparib vs placebo). The benefit of maintenance PARPi extends beyond *BRCA1* and *BRCA2* mutations and HRD. Following the results of the phase 3 NOVA study,[101] niraparib received FDA approval as maintenance treatment of patients with platinum-sensitive recurrent EOC who have achieved a complete or partial response following platinum-based chemotherapy regardless of *BRCA* status. Patients treated with niraparib had a significantly longer median PFS than did those given placebo, including 21·0 months versus 5·5 months in the germline *BRCA1* or *BRCA2* cohort (HR 0·27, 95% CI 0·17–0·41), as compared with 12·9 months versus 3·8 months in the non-germline *BRCA1* or *BRCA2* cohort for patients who had tumours with HRD (0·38, 0·24–0·59) and 9·3 months versus 3·9 months in the overall non-germline *BRCA1* or *BRCA2* cohort (0·45, 0·34–0·61; p<0·001 for all three comparisons). The most recent addition to the pharmacopeia has been rucaparib, which showed significant benefit for maintenance therapy following a good response to platinum-based chemotherapy following recurrence.[102] Median PFS in patients with a *BRCA*-mutant carcinoma was 16·6 months (95% CI 13·4–22·9) in the rucaparib group versus 5·4 months (3·4–6·7) in the placebo group (HR 0·23 [95% CI 0·16–0·34]; p<0·0001); in patients

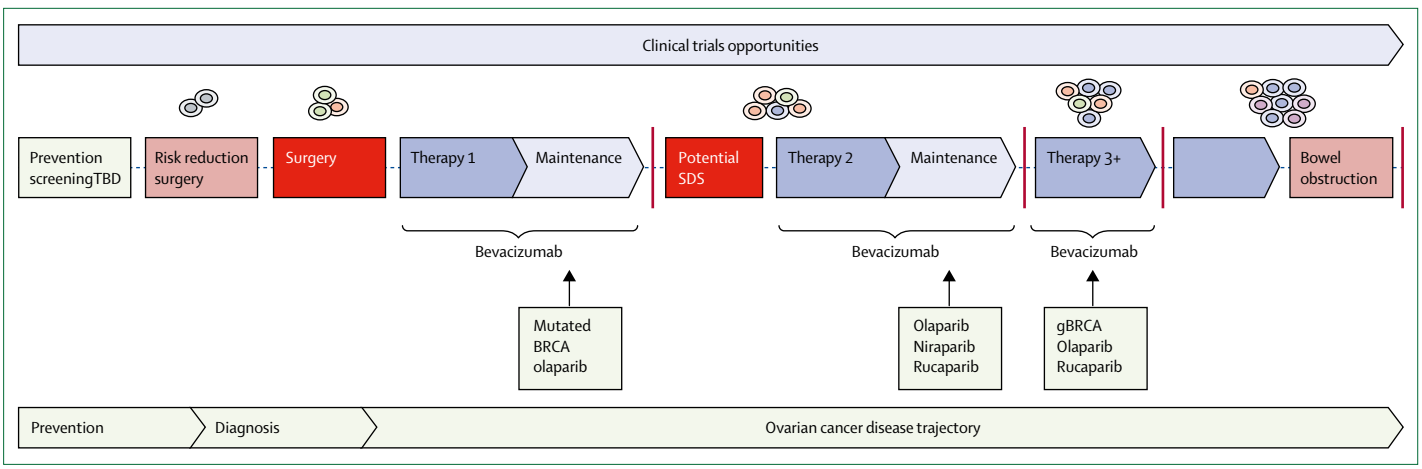

Figure 5: **Disease evolution and treatment opportunities in ovarian cancer**
Combination therapy targeting DNA damage response, cell-cycle, signalling pathway, and tumour microenvironment might be required to control the profound genomic complexity of evolution of HGSOC. Bevacizumab is a vascular endothelial growth factor inhibitor, whereas olaparib, niraparib, and rucaparib are poly ADP-ribose polymerase inhibitors. The vertical red lines represent the time of recurrence. SDS=secondary debulking surgery. TBD=to be determined. HGSOC=high-grade serous ovarian cancer.

with an HRD carcinoma, it was 13·6 months (10·9–16·2) versus 5·4 months (5·1–5·6; HR 0·32 [0·24–0·42]; p<0·0001).

Collectively, the greatest benefit of PARPi as single agent therapy has been observed in women with HGSOC containing deleterious germline or somatic mutations in *BRCA1* or *BRCA2*,[103] followed by women with evidence of HRD; however, biomarkers have not been specific enough to predict benefit. Novel strategies are underway to avoid the use of chemotherapy and involve combination of targeting drugs, such as olaparib and cediranib,[104] regardless of *BRCA1* and *BRCA2* status at the time of platinum-sensitive relapse.

Recurrent disease follows a frequent relapse–response pattern before becoming resistant to treatment. For platinum-resistant disease, various sequential mono-chemotherapies including weekly paclitaxel, liposomal doxorubicin, and gemcitabine are used until subsequent progression or unacceptable toxicity. However, as the expected response rate in the platinum-resistant setting is low (about 10–15%), several trials are investigating new agents to overcome resistance.[105] In the platinum-resistant setting, a phase 3 trial (AURELIA)[106] showed that addition of bevacizumab to various chemotherapy regimens increased the PFS from 3·4 months to 6·7 months (HR 0·48, 95% CI 0·38–0·60; unstratified log-rank p<0·001). An unplanned exploratory subgroup analysis reported that the PFS benefit was greatest in the weekly paclitaxel group, with an improvement from 3·9 months to 10·4 months with addition of bevacizumab.

Patients with refractory disease, defined as progression during the first line of platinum-based chemotherapy, have a very poor prognosis with very low response rate to standard chemotherapy. These patients are often excluded from trials and there is an urgent need to define options for this group.

Future directions

After the approval of anti-angiogenics and PARPi, there is an active interest in combination therapy to overcome resistance. Acquired drug resistance mechanisms to PARPi involving *BRCA* mutation reversions and *ABCB1* fusions are well known but they are often not present in all tumour cells,[107,108] suggesting that multiple resistance mechanisms might be present within an individual patient. Research aimed at delineating novel resistance mechanisms is needed. Another area of investigation is the immune infiltration and tumour hypoxia,[109] and how modulating the microenvironment might prompt responses to therapy. Because preliminary results of immunotherapy as single agent showed low response rates in HGSOC,[110] novel approaches are based on combination strategy and T-cell therapy. [111]

Efforts are also ongoing to improve drug delivery; antibody-drug conjugates are an important class of highly potent biopharmaceutical drugs designed as a targeted therapy. Antibody–drug conjugates consist of an antibody designed against a specific target linked to a cytotoxic agent.[112] Because targets do not have to be drivers of tumour growth, antibody-drug conjugates are an emerging class of therapeutics, particularly in ovarian cancer without clear oncogenic drivers. As an example, Mirvetuximab soravtansine (IMGN853) consists of a humanised anti-folate receptor monoclonal antibody attached to the cytotoxic maytansinoid DM4.[113] This targeted therapy with IMGN853 is being assessed in the phase 3 trial for patients with folate receptor-positive platinum-resistant EOC. The antibody-drug conjugate strategy offers the possibility to investigate functional imaging based on the identification of the target and tissue analysis.[114]

The challenge is to define the appropriate combination and sequence strategy for a patient at a specific time and

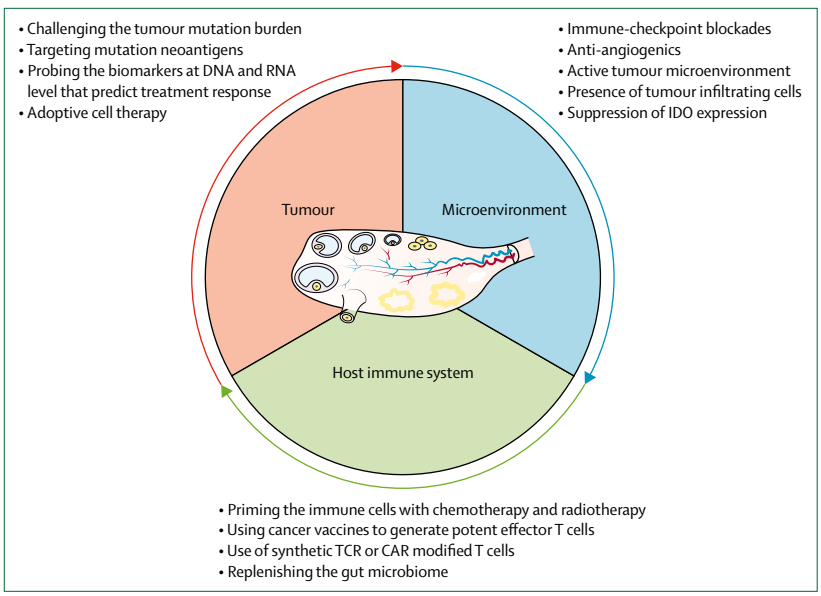

Figure 6: **Different immunotherapeutic strategies in targeting ovarian cancers**
This strategy ranges from targeting the ovarian cancer cells, or the tumour microenvironment, or boosting the host immune system. IDO=indoleamine-pyrrole 2,3-dioxygenase. TCR=T-cell receptor. CAR=chimeric antigen receptor.

then identify mechanisms of resistance that will guide the treatment tailored to each patient.

Patient journey: evolution of disease

In HGSOC, *TP53* mutation is followed by multiple sequential mutational processes that drive the pathogenesis into a highly complex, genomically unstable tumour with low frequency of oncogenic mutations and few recurrent copy number alterations.[115] These aberrations can evolve with time and exposure to different lines of treatment, increasing the risk of developing therapeutic resistance. Majority of targetable mutations are concordant over time, despite intercurrent chemotherapy and associated clonal selection.[116] However, reversion mutations restoring the open reading frame of *BRCA* have been described with PARPi treatment,[117,118] and recovery of BRCA protein expression,[119] which predict for resistance to therapy.[120] Whole genome sequencing has established the potency of the somatic genome, characterised with diverse DNA repair deficiencies that can be used to stratify ovarian cancers into distinct biological groups with predictive signatures of resistance or relapse.[121] Next-generation sequencing is further facilitating a deeper understanding of resistance and response; in particular, the analysis of exceptional responders in clinical practice allows for discovery of predictive signatures that might revitalise or reposition the use of targeted agents.[122] Unique genomic determinants might be associated with the exceptional outcome in HGSOC patients; concurrent homologous recombination deficiency and RB1 loss were associated with favourable outcomes, suggesting that co-occurrence of specific mutations might mediate durable responses.[123] Spatial and temporal intra-tumour heterogeneity is a major challenge for the development of precision medicine and treatment.[124–126] Several new targets have been identified for each tumour type and are under evaluation as part of clinical trials (figures 2–4). Given the complexity involved in the mechanisms of therapeutic resistance, the characterisation of the disease processes at recurrence is key to identify the best treatment strategy for a patient at that time (figure 5). Combination therapy targeting DNA damage response, cell cycle, signalling pathway, and tumour microenvironment might be required to control the profound genomic complexity of evolution of EOC. This combination therapy involves a change in practice and a need for sequential biopsy, or liquid biopsy, to define the mechanism of resistance involved in the current episode of recurrence. Studies have shown the feasibility to detect reversion mutations in circulating tumour DNA on resistance to therapy, suggesting its potential clinical use.[118,127] Circulating tumour cell collection has shown real-time molecular characterisation of drug response at multiple timepoints in some cancers.[128]

The cellular, molecular, and spatial heterogeneity of ovarian cancer has led to very active consideration of harnessing the immune system to target this disease (figure 6). Tumour infiltrating lymphocytes are associated with improved clinical outcome in EOC patients;[129–131] prognostic subtypes have also been suggested.[76,132] Early studies have incorporated interventions with immune checkpoint blockade, cancer vaccines, and adoptive cell therapy. Initial trials included all subtypes of EOC, and response rates appear to be modest with checkpoint inhibitors as single agent in HGSOC with some encouraging activity seen in clear-cell ovarian cancer.[133–136] Beyond the PD-1 and CTLA-4 pathways, additional tolerogenic mechanisms can be targeted and used in combination with immune therapies, such as chemotherapy or anti-angiogenics. The hypothesis that immune targeted therapy in combination with chemotherapy or molecular targeted agents will improve immune exposure of and activity of EOC has led to the emergence of many beforementioned combination options as well as randomised clinical trials in first-line and recurrent treatment settings.

Quality of life and symptom management

Given the potential chronicity of EOC, patients might experience a multitude of relapses and treatment-related adverse events that can affect quality of life. Efforts are ongoing to integrate this endpoint into clinical trials and design studies in recurrent disease in which the patient reported outcomes are major endpoints.[137] At the time of recurrence, the goal of treatment is to control the disease and maintain quality of life. This goal means that treatments have to ensure an acceptable safety profile and balance symptom benefit with risks, particularly in the platinum-resistant setting.[138] To incorporate a patient's perspective on

side-effects, patient reported outcomes have been integrated into standard reporting of adverse events based on Common Terminology Criteria for Adverse Events.[139,140]

Malignant bowel obstruction is the most common complication of EOC progression and is described by patients as the most devastating event experienced over their disease trajectory with a median survival of less than 5 months.[141] This complication is a major clinical challenge because of the few therapeutic options associated with substantial symptoms, such as the inability to maintain oral intake, vomiting, and abdominal pain, which lead to nutrient deprivation. Malignant bowel obstruction management is not well defined and includes potential surgical or radiology intervention, medical support, and the ethical dilemma of total parenteral nutrition. Efforts are ongoing to offer a multidisciplinary management including surgery, chemotherapy, radiation, interventional radiology, and to include patients' preferences.[142,143] In this setting, the question of total parenteral nutrition is difficult because the selection of patients who will benefit from total parenteral nutrition is not well described and the majority of patients will die from cancer progress, not starvation.[144] Early intervention of palliative care is also important to improve patient care.[145,146]

Conclusion

Efforts towards better understanding and characterising the different types of EOC have been leveraged into new therapies, transitioning to standard of care. Discovery research is advancing into hypothesis-driven trials and translational research. Access to clinical trials and international collaboration has been crucial in this progress, particularly for the rare tumour types. Building a strong multidisciplinary network with the integration of discovery research with clinical practice is key to improve precision medicine that will affect patient care. The delivery of value-based and patient-centred care is paramount in improving outcomes as is learning from each patient, from treatment responders to refractory patients. The value of cancer treatment is based on clinical benefit, toxicity, and improvements in patient symptoms or quality of life in the context of cost.[147] Patient engagement and input should be integrated to make these efforts meaningful and measurable.

Contributors

SL wrote the summary; introduction; the sections on HGSOC, future direction, disease evolution, and patient management; and had an editorial overview of the entire manuscript and revised it for final publication. CG wrote the rare histology subtype section of EOC, had an editorial overview of the entire manuscript, and provided expertise on the direction and management of ovarian cancer. IV wrote the part on surgical management of EOC and reviewed the manuscript. AMO did the seminar design and overview, provided scientific expertise, guidance, and support in the manuscript writing; reviewed all the data; and had an editorial overview of the entire manuscript.

Declaration of interests

We declare no competing interests.

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